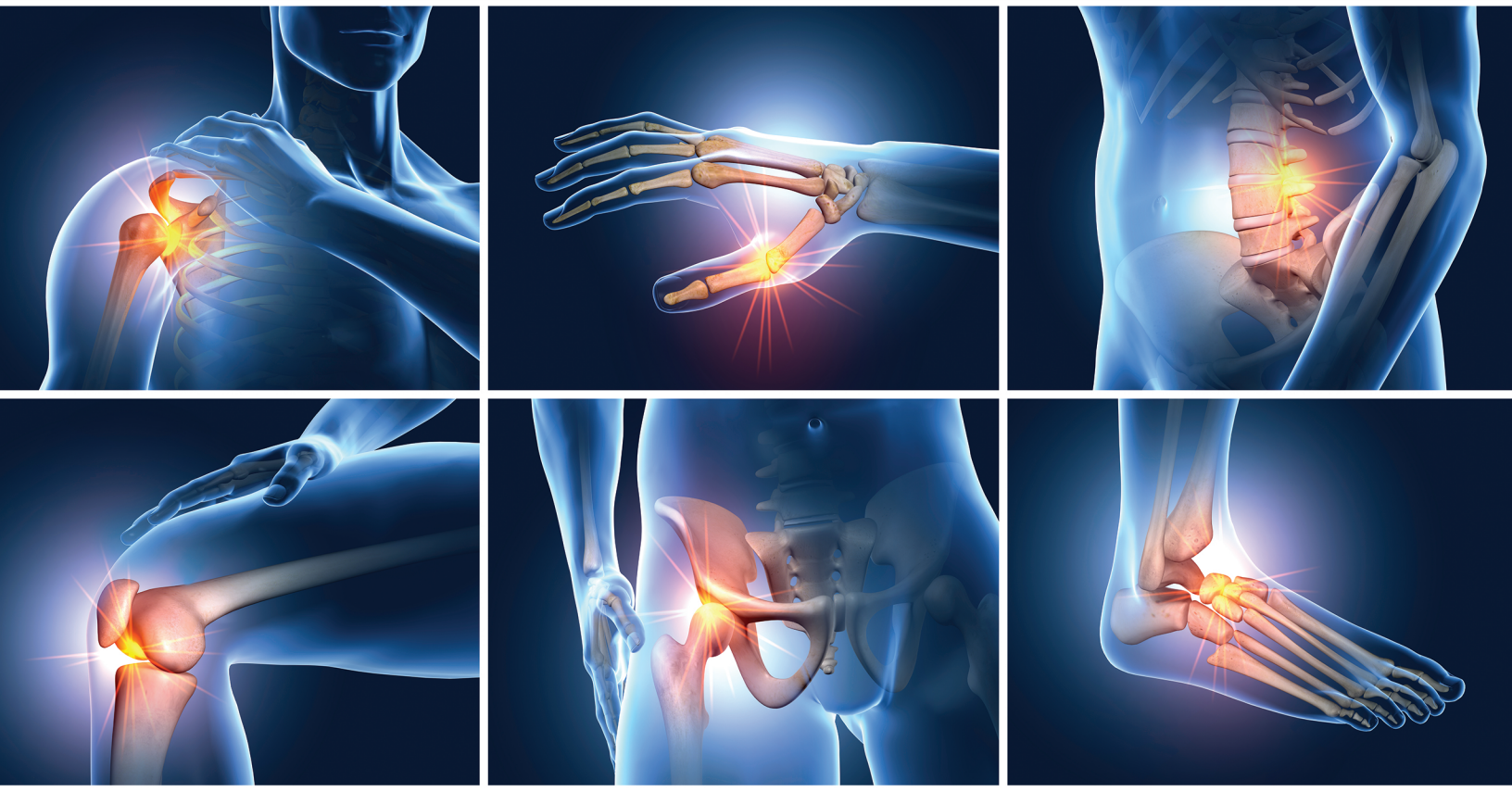
OSTEOPOROSIS, OSTEOARTHRITIS AND RHEUMATOID ARTHRITIS: AN AGONIZING SKELETAL TRIAD



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Osteoporosis, Osteoarthritis and Rheumatoid Arthritis: An Agonizing Skeletal Triad

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PREFACE

This book is about three formidable skeletal diseases; osteoporosis, osteoarthritis and rheumatoid arthritis, which are severely threatening the public health system and increasing the chronic disease burden. Identification and prevention of this agonizing triad are complex, composite and complicated, as several molecular culprits collaborate and contribute to their development and progression. Fragile, flamed and fractured elements of bone affiliated to these disorders have been examined from several perspectives but contradictions and controversies have further amassed to their complexity. This family of skeletal triad has many uninvited and unsolicited related effects in the form of pain, stress and anxiety that their remedial prescriptions to get rid of them become confusing and perplexing. Commoners perceive these health issues either casually or as artefact of misconceived notions and fall prey to unqualified quacks and half-baked practitioners. It is equivocally accepted that there are many underlying mechanisms and mediators that commonly as well as individually influence the pathology of osteoporosis, osteoarthritis and rheumatoid arthritis. Recent scientific work has identified some frightful perpetrators and their *modus operandi* in the initiation, development and progression, but the troubled bones demand further investigations.

The present eBook, "Osteoporosis, Osteoarthritis and Rheumatoid Arthritis: An Agonizing Skeletal Triad" intends to bring together insightful leads on the latest news, views, and reviews from authors, scientists, and clinicians from different regions of the world on these skeletal abnormalities. This compendium is a sincere effort to have input of internationally acclaimed scholars and thinkers to reveal those cellular and molecular culprits who participate but are absconding from the scene of pain and suffering posed to our elderly population afflicting them by these musculoskeletal problems.

In the first chapter, "Osteoporosis and Chronic Liver Disease", the author Yi-Liang Tsai, sheds light on the close inter-relationship of chronic liver disease with osteoporosis. A substantial percentage of chronic liver disease patients suffer from osteoporosis because of disturbed calcium homeostasis. The liver is an important organ that plays a crucial role in several physiological, metabolic and immune-related processes. Composed of hepatocytes, biliary epithelial cells, stellate cells, kupffer cells and hepatic sinusoidal endothelial cells, the liver controls endocrine growth signaling pathways, blood volume regulation, cholesterol homeostasis, nutrient metabolism, and immune system regulation. The role played by the liver in distressed form causing disturbed calcium homeostasis and dysregulated nutrient balance in relation to bone mass has been elaborated on in this chapter.

The second chapter, "Detection of Knee Osteoarthritis using Artificial Intelligence" enriches our knowledge regarding the identification of knee osteoarthritis with artificial intelligence. Knee osteoarthritis is a degenerating joint disorder that affects joints and causes functional disability and pain if left untreated. Therefore, the identification of knee osteoarthritis at an early stage is crucial for better management and prevention, but early identification is complicated, confusing, and sometimes missed. It is envisioned and analysed by Thongpat and co-authors in this chapter that artificial intelligence involving a Convoluted Neural Network (CNN) can predict the early stage of knee osteoarthritis. Such a wonderful effort can substantiate the already existing identification techniques (Kellgren Lawrence grading) from radiographic images that hold a promising future in the direction of better prognosis, diagnosis and therapeutic modalities of knee osteoarthritis.

The third chapter, "Role of Cytokines and Chemokines in Rheumatoid Arthritis" exhibits the details of inflammation, which is the chief culprit in rheumatoid arthritis. Rheumatoid arthritis

is a chronic auto-inflammatory disease having progressive cartilage deterioration, synovial inflammation and periarticular calcium erosion. The causes are multifactorial and complex which have fostered diverse therapeutic modalities for its remission, which is possible but challenging because of heterogeneous symptoms, late referrals, or mimicking with other pathologies. A better understanding of the ways that inflammatory mediators trigger and propagate the deterioration of joints is imperative for developing efficient treatments. In the pursuit of a better understanding of inflammation in rheumatoid arthritis, the role and relevance of cytokines and chemokines must be probed as cellular and molecular determinants. Details of some such pro-inflammatory mediators; tumour-necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), IL-8 along with CC chemokines (CCL2, CCL3, CCL4 and CCL5) and CXC chemokines (CXCL5, CXCL8, CXCL9 and CXCL10) have been reported in this chapter.

The fourth chapter, “Vitamin D and Immune System: Implications in Bone Health” has introduced that the host immune system interacting with vitamin D plays a significant role in maintaining calcium and mineral turnover along with the preservation of bone strength. Vitamin D supplementation helps in absorbing calcium, and bone minerals and has great immunomodulatory potential, which not only serves as a guard against bone resorption but also facilitates healing and repair. The showcasing of the importance of vitamin D through the interaction of the immune system and maintenance of calcium homeostasis within the scenario of osteoimmunology is wonderfully presented.

In the fifth chapter, “Bone Water: Effects of Drugs on Bone Hydration Status”, Dr. Khan reviewed an unforeseen but important aspect of bone hydration. Water is a crucial nutrient that constitutes approximately 20 percent of the cortical bone by volume. It influences mechanical properties, agility and quality of bone whereas, bone dehydration can stimulate stress-induced deformity (modulus of elasticity). The ill effects of bone dehydration increase manifold in elderly individual where dehydration of the bone interacts with frailty and cause fragility of the bone leading to susceptibility to fractures. The author has shown that bone dehydration also supplements disease severity and worse outcomes in diseases like diabetes, osteoporosis, and osteogenesis. Drugs also induce hypo-hydration of the bones and the interaction between drugs and bone water *vis-à-vis* skeletal health has been highlighted in this chapter.

The sixth chapter, “Dietary Patterns and Rheumatoid Arthritis” has exhibited the importance and necessity of a balanced diet to resist the formidable pangs of pain and suffering in rheumatoid arthritis. The authors have highlighted different forms of diets and dietary patterns and have explained their pros and cons in the pathology of rheumatoid arthritis. It is proposed that a good balanced diet can regulate the underlying inflammatory and immunomodulatory pathways influencing the disease's severity and its outcome.

Chapter seven,” Self-perceived Quality of Life in South Asian and British White Rheumatoid Arthritis Patients in the East Midlands, UK” has investigated the heterogeneity of pain, pain-affiliated disease severity and quality of life in rheumatoid arthritis patients of South Asia and British White residing in East Midlands, UK. The analysis of self-perceived quality of life between these two groups has revealed that reduced mobility and physical activity are associated with higher pain perception in South Asian rheumatoid arthritis patients. Such studies have important implications for setting interventional guidelines for pain-resolving treatment outcomes as an individual’s culture, education, financial situation, diet, and family support have a strong impact on pain realization and perception.

I am deeply indebted to Mr. Nitin Kumar and Ms. Srishti Valecha for their extended help in the style editing of the book. I extend my heartfelt gratitude to Ms. Noor ul Ain Khan, Manager Publications, Mr. Obaid Sadiq, Manager, Mrs. Humaira Hashmi, Editorial Manager Publications and especially Mr. Mahmood Alam, Director Publications, Bentham Science Publishers for their kind support, encouragement and help.

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DEDICATION

To my loving God, who lovingly gave me two lovable gifts: My Wife and Son

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CHAPTER 1

Osteoporosis and Chronic Liver Disease

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Abstract: The liver is composed of hepatocytes, biliary epithelial cells, Kupffer cells, stellate cells, and hepatic sinusoidal endothelial cells. It also plays an important role in the digestive system and immune system at the same time. The different types of hepatitis, including viral liver diseases, autoimmune liver diseases, and metabolic liver diseases, are all closely related to osteoporosis. People with liver disease have a significantly higher risk of developing osteoporosis than people without hepatitis. Fibrosis is part of the wound-healing response that maintains organs after tissue injury, but excessive fibrosis may also contribute to a variety of human diseases. Hepatic stellate cells are the key to liver fibrosis. The apoptotic hepatocytes stimulate fibrosis in hepatic myofibroblasts, and activated hepatic stellate cells are the main source of myofibroblasts in the liver. Activated hepatic stellate cells possess many voltage-operated calcium channels. Changes in the concentration of calcium ions mediate hepatic stellate cell activation and fibrosis regression. The skeleton is one of the main regulatory mechanisms of calcium ions in the body. Therefore, chronic hepatitis leads to a disturbance of calcium homeostasis *in vivo*, which may be one of the factors causing bone loss.

Keywords: Autoimmune liver disease, Bone mineral density, Fibrosis, Metabolic liver disease, Osteoporosis, Viral liver disease.

INTRODUCTION

There are three main causes of osteoporosis caused by chronic kidney disease: abnormal calcium and phosphorus metabolism, vitamin D deficiency, and secondary hyperparathyroidism. Parathyroid hormone (PTH) can activate osteoclasts to break down bone, release calcium ions and increase blood calcium concentration. When PTH acts on the kidney, it helps the kidney to produce vitamin D and increase calcium reabsorption [1, 2]. Low vitamin D levels stimulate PTH production, but high vitamin D levels do not always lead to low

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PTH levels. Serum PTH levels will be low and stable when vitamin D is above 30 ng/mL [3 - 5].

Both chronic kidney disease and chronic hepatitis are known to increase the risk of osteoporosis. The common causes are disturbed calcium metabolism and vitamin D deficiency.

The liver is an important organ that maintains the normal life activities of the body and is a key hub for many physiological processes. It is composed of hepatocytes, biliary epithelial cells, stellate cells, Kupffer cells, and hepatic sinusoidal endothelial cells. Its functions include controlling endocrine growth signaling pathways, blood volume regulation, lipid and cholesterol homeostasis, breakdown of exogenous compounds, and nutrient metabolism (carbohydrates, lipids and proteins) [6].

In addition, the liver plays an important role in the immune system. Overexpressed inflammation leads to tissue damage and remodeling, and chronic inflammation when immunity is compromised [7]. In chronic liver disease, viral, toxic, metabolic, or autoimmune triggers lead to hepatocyte death, followed by inflammation and compensatory proliferation, associated with the development of fibrosis, cirrhosis, and even hepatocellular carcinoma [8].

OSTEOPOROSIS & LIVER DISEASES

Vitamin D not only plays an important role in regulating bone, calcium, and phosphate metabolism [9], but also plays a key role in liver diseases. Vitamin D deficiency is often observed in chronic liver diseases, including hepatitis B virus [10, 11], hepatitis C virus [12, 13], and non-alcoholic fatty liver disease [14, 15]. Osteoporosis is a common complication in patients with chronic liver disease, with a prevalence ranging from approximately 4% to 21% [16]. It is currently known that liver diseases predisposing to osteoporosis include viral liver diseases (hepatitis B and hepatitis C), autoimmune liver diseases (ALD) (autoimmune hepatitis (AH), primary biliary cirrhosis (PBC), and sclerosing cholangitis) and metabolic liver diseases (alcoholic hepatitis and non-alcoholic fatty liver disease).

Viral Liver Disease

Both hepatitis B virus (HBV) and hepatitis C virus (HCV) are hepatotropic viruses. HBV is a partly double-stranded DNA virus [17]; HCV is a single-stranded RNA virus [18]. The main route of infection is the virus-infected blood and body fluids entering human body, through the skin or mucous membranes, especially the blood.

Hepatitis B Virus

The cross-sectional study of Chen *et al.* assessed the association between the patients with HBV infection and bone mineral density (BMD) using a multiple linear regression model. The covariates are age, gender, body mass index, proteinuria, serum total cholesterol, uric acid, creatinine, glutamic-oxaloacetic transaminase, albumin, C-reactive protein, thyrotropin, history of smoking and drinking. The results of the fully adjusted model have shown that HBV infection is significantly negatively correlated with BMD (β= -0.17, $p<0.05$) [19].

Another 12-year longitudinal study has assessed the association between HBV infection and osteoporosis risk. Of 180,730 patients admitted, 36,146 and 144,584 patients were divided into an HBV-infected group and a control group, respectively. The factors adjusted in the model included age, gender, frequency of hospital visits, hypertension, diabetes, hyperlipidemia, heart failure, liver cirrhosis, chronic kidney disease, thyroid disease, steroid drugs, warfarin, proton pump inhibitor, aspirin and estrogen replacement therapy. Compared with the control group, the HBV-infected group had a 1.13-fold higher risk of developing osteoporosis [20].

In the terms of vitamin D, low serum $25(OH)D_3$ levels are associated with high levels of HBV replication in patients with chronic hepatitis B [21]. HBV can utilize multiple mechanisms to increase intracellular Ca^{2+} concentration, creating a cellular environment to facilitate its infection [22].

A prospective study by Mohamed *et al.* has reported a change in serum $25(OH)D_3$ levels in chronic hepatitis B patients before and during antiviral therapy. A total of 50 treatment-naive chronic HBV patients and 30 healthy subjects were enrolled in the study. The cases received treatment in the form of Lamivudine 100 mg tablet, once daily. Serum $25(OH)D_3$ levels were assessed twice, once before initiation of antiviral treatment and again at least 6 months later. The studied cases showed significantly low mean serum vitamin D levels when assessed before treatment (21.6 ± 5.8 ng/ml) as compared to the levels after 6 months of treatment (31.1 ± 7.3 ng/ml) which was comparable to that of the control group (33.4 ± 5 ng/ml) [23].

Hepatitis C Virus

69 chronic HCV-infected participants were enrolled in a prospective cohort study. The results showed that the mean BMD, Z-score, and T-score of the lumbar spine in patients with chronic hepatitis C were significantly lower than the control group without chronic hepatitis C ($p<0.001$). The results also showed that bone alkaline phosphatase and the C-terminal cross-linked telopeptide of type I

CHAPTER 2

Detection of Knee Osteoarthritis using Artificial Intelligence

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Abstract: Knee osteoarthritis (KOA) is a common degenerative joint disease that results in disability due to joint dysfunction and pain. Almost one-fifth of early KOA cases are missed during the routine practice resulting in the progression of the disease. This narrative review aimed to explore and analyze various literatures that proposed Convoluted Neural Network (CNN) model in detecting KOA and its severity based on Kellgren Lawrence grading classification. At first, 221 publications were retrieved using the search term "artificial intelligence" and Knee osteoarthritis". Only studies that used CNN and radiographic images were included in this study in which only 14 studies fitted our inclusion criteria. Each paper was thoroughly investigated for the input data and CNN model adopted as well as the performance and limitation of that study. Lastly, the conclusion was made and discussed using these results. Object detection and Classification models were among the most popular techniques adopted. Our results showed that object detection models were overall superior regarding the accuracy in the detection of KOA and its severity. The application of CNN for the detection of KOA from radiographic images has shown great promise where each technique has its own advantage. In the foreseeable future, the combination of object detection and classification detection may provide excellent potential as a merit tool to help orthopedists and related physicians for the proper diagnosis and treatment of KOA.

Keywords: Artificial intelligence, Knee osteoarthritis, Radiographic image.

INTRODUCTION

Knee osteoarthritis (KOA) is a degenerative joint disease that causes pain and restricted range of motion which may lead to a decline in the quality of life [1 - 3]. It is a chronic disorder typically known as a result of wear and tear processes leading to progressive destruction of the articular cartilage and, ultimately, functional disability [4]. The symptom of knee pain during weight-bearing activities is one of the earliest signs [5]. If left untreated, it could progress to

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disability due to the decrease in range of motion (ROM) of the knee and the inability to walk. The current definite mainstay treatment for advanced-stage KOA is knee joint replacement which is costly and places a huge burden on the overall healthcare cost [6, 7]. With this, the focus of treatment has been shifted towards prevention and treatment during the early stage [6, 7]. Although early intervention can prevent further degeneration, up to 15% of early KOA are left undetected during routine practice [8, 9]. Due to the recent emergence of Artificial Intelligence (AI), there has been a growing trend in its application in tackling medical problems. The detection of KOA with the adoption of AI may help physicians in detecting and localizing pathological lesions of the knee.

AI was first defined as the ability of a machine to learn and solve problems. With its complex algorithm-based processing, it allows machines to learn by using hidden layers (decision tree) making it applicable in many fields of medicine [1]. A convolutional neural network (CNN) or deep learning system is a sophisticated technique that mimics the human nervous system by including many layers of processing. These layers include the input layers, hidden layers and the output layers, which allow the identification of complex patterns in comparison with traditional machine learning techniques [10 - 13]. Due to CNN's fast processing ability, it can be used for real-time detection of the desired object in an image or video, a technique known as Computer vision. Many previous studies have demonstrated the usefulness of CNN in aiding the diagnosis of many diseases from various diagnostic investigations, including histological imaging, radiographic imaging and magnetic resonance imaging (MRI). The detection of pathologic lesions in KOA is a prime example of how AI could assist physicians [5, 10 - 22].

There has been much research conducted on machine learning in the past that aims at assisting physicians in the diagnosis of diseases. Algorithm-based machine learning using patient information such as age, patient history, risk factors, and predisposing illness can help predict the outcome of the disease [12]. Currently, there has been growing popularity in the field of computer vision to detect pathological lesions shown in radiography. The AI-assisted methods have been increasingly implemented in diagnosing and treating KOA. This review aims to present the potential of AI, as well as its limitations, in the detection of KOA using radiographic imaging.

MATERIAL AND METHODS

First, we retrieved a total of 221 studies from PubMed and Google Scholar published between 2000 and 2021. The search keywords used were "artificial intelligence and knee osteoarthritis". Then further screening was performed,

where articles that were published in the English language, had full text, contained keywords of radiographic images and adopted CNN were included for this review. Exclusion criteria were articles that were not written in the English language, published before the year 2000 and studies that were conducted with MRI or CT images and used shallow machine learning algorithms. Duplicates were also excluded. Finally, only 14 publications were selected for this narrative review. The workflow of the identification of studies is shown in Fig. (**1**).

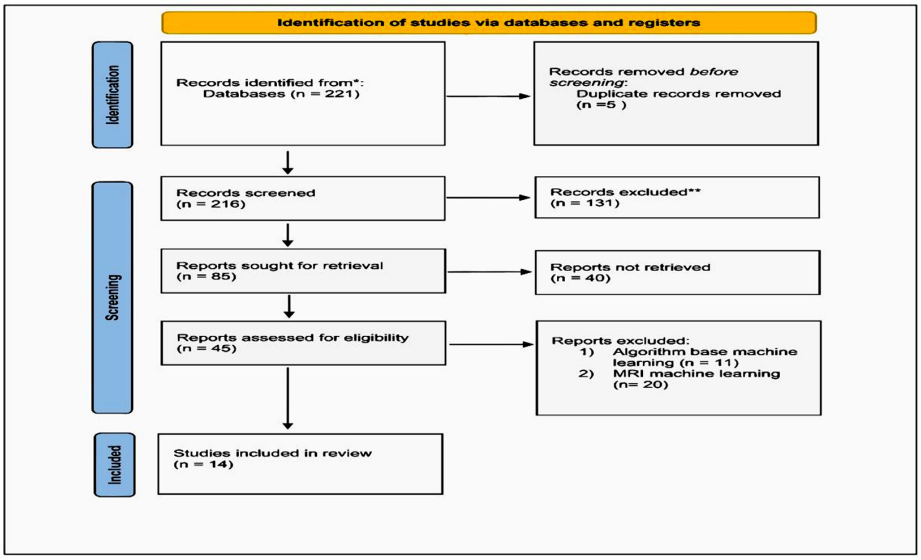

Fig. (1). Identification of studies.

The learning algorithm, model validation method, results and limitations of each individual study were explored. Then, these parameters were compared and analyzed. Lastly, the result of our analysis was discussed and concluded.

DETECTION OF KNEE OSTEOARTHRITIS BY AI

Detection of KOA using AI can be helpful for medical practitioners during their daily practices. However, there are challenges associated with training the AI. Even though many individuals might have similar body structures, no two people are exactly identical, and this is certainly true for the structure of the knee [5]. In building the basis for AI training, consistency of information is critical. If the information is not consistent, AI would need a greater amount of input information to provide a satisfactory result in terms of detection performance. In KOA radiography, the pathological presentations are osteophytes, subchondral bone sclerosis, and bone structure which may display great variations among different individuals. This may pose a great hurdle in the training of the deep

CHAPTER 3

Role of Cytokines and Chemokines in Rheumatoid Arthritis

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Abstract: Rheumatoid arthritis (RA) is a chronic, inflammatory, and destructive polyarthritis with numerous autoimmune features and the potential for extra-articular and systemic complications. Much progress has occurred in defining important mechanistic components of RA, leading to significant advances in its treatment. RA is a multifactorial and multistage disease, beginning with preclinical autoimmunity that arises in a genetically predisposed individual who encounters one or more environmental triggers, progressing to the clinical appearance of inflammation in joints and sometimes in other organs, and leading to destruction of the articular cartilage and adjacent bone. Regulatory role in inflammation, autoimmunity and articular destruction in the joints of rheumatoid arthritis patients is played primarily by chemokines and cytokines. Amongst many top players of inflammation in RA, tumour-necrosis factor-alpha (TNF-α) is counted as the chief culprit. It is produced by synovial macrophages, B lymphocytes, and NK-cells. Furthermore, TNF-α has exhibited to be of particular utility as a therapeutic target. IL-17A is synthesized by T helper 17 (Th17), which initiates the generation of inflammation causing cytokines like interleukin-6 (IL-6), IL-8 and GM-CSF by cells of endothelium, epithelium and fibroblasts and localization of neutrophils. Progression of inflammation in the synovial fluid is augmented by chemokines in the joints of rheumatoid patients. Elevated levels of CC chemokines (CCL2, CCL3, CCL4 and CCL5) and CXC chemokines (CXCL5, CXCL8, CXCL9 and CXCL10) have been reported in such patients. Moreover, these chemokines may control cell trafficking directly by interacting with their cognate receptors present on inflammatory cells and also by modulating angiogenesis. Several proinflammatory cytokines and chemokines participate in many biological pathways finally setting the loop of inflammation and exacerbation of the outcome and these serve as biomarkers for a number of autoimmune and inflammatory disorders.

Keywords: Rheumatoid arthritis, Cytokines, Chemokine.

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INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by a communication between innate and adaptive immune cells and mediators. Such cellular cross talks are responsible for triggering systemic as well as local at different phases of this disease. It has been documented that almost 0.2-1 percent of North Americans and Europeans are suffering from RA, however, considerable regional variation is noticed. Moreover, incidence rates for RA were observed to be approximately 500 patients per 100,000 populations with considerable geographical incongruity [1].

In recent years, researchers have made significant progress in understanding the mechanisms involving cells from both the innate and adaptive immune systems, such as monocytes and macrophages [2, 3]. By orchestrating various inflammatory and tissue remodeling pathways, many soluble and membrane-bound mediators play important roles in this cross-talk [4, 5].

Inflammatory cytokines are capable of activating destructive mechanisms in the joint, resulting in structural damage and, as a result, a functional reduction in mobility which ends with disability [6]. The complicated interactions of inflammatory cytokines are responsible for joint injury that begins at the synovial membrane and proceeds to other joint tissues [7]. There is widespread activation of monocytes, macrophages, and synovial fibroblasts, as well as an increase in the production of proinflammatory cytokines such as Interleukin 1(IL-1), Interleukin 6(IL-6), and Tumor-necrosis factor-alpha (TNF-α) [8]. Other cytokines and chemokines that are detected in the synovial membrane include Interleukin 15 (IL-15), Interleukin 17 (IL-17), and Interleukin 18 (IL-18). These inflammatory cytokines activate various signaling pathways and stimulate gene transcription, which are important factors in inflammation and the degradation of the tissue [9].

The inflammation causing cytokines are the key targets to control RA. TNF-targeting has been shown to be effective in the treatment of RA using either customized cytokine antibodies or used as receptors for soluble cytokines as decoys. Pro-inflammatory cytokine activity can even be inhibited by small molecule inhibitors of cytokine signaling or by utilizing targeted short interfering RNA (siRNA) to suppress the expression of a specific cytokine [10].

B cells in the peripheral blood of RA patients can secrete many cytokines including Chemokine (C-C motif) ligand 3(CCL3), TNF-α, Interferon gamma (IFN-γ), IL-6, Interleukin-1β (IL-1β), IL-17, and IL-18. TNF-α can increase the expression of receptor activator of nuclear factor-κB ligand (RANKL) by B cells in the presence of IL-1β, thereby promoting the formation of osteoclasts [11, 12] (Fig. **1**). Regulatory B (Breg) cells are a type of B cells that exert immuno-

suppressive functions. Breg cells are mainly responsible for the production of anti-inflammatory cytokines (IL-10, TGF-β, and IL-35) [13].

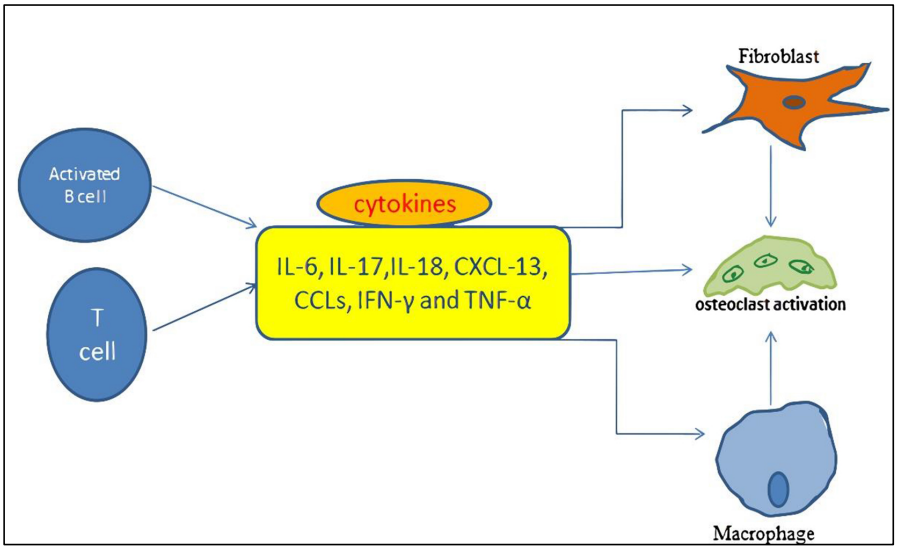

Fig. (1). Cytokine secretion by B cells in RA.

ROLE AND RELEVANCE OF CYTOKINES IN RA PATHOGENESIS

Cytokines play a pivotal role in the development of RA inflammation due to their role as signaling molecules between immune cells and tissue cells. TNF-α, IL-17A, IFN-γ and receptor activator of nuclear factor κB ligand are the most common but prominent cytokines formed by invading T cells (RANK-L) [14].

Amongst many top most promising mediators of joint inflammation in RA, TNF-α is counted as chief culprit. It is produced by synovial macrophages, B-cells, and Natural killer (NK) cells. TNF-α is found largely in biopsy specimens of arthritic tissue and its exaggeration causes natural inflammation in a variety of mouse models of arthritis. It may cause severe degradation of cartilage and bone, according to early *in vitro* investigations [15].

TNF-α has been found to induce osteoclast genesis by increasing RANK-L production by osteocytes. According to some studies, it may also directly drive the development of monocyte/macrophage lineage cells into osteoclasts *via* a RANK-L-independent mechanism [12, 16]. The potential of TNF-α to increase the production of other inflammatory cytokines, such as IL-1β and IL-6, which invite leukocytes and encourage the creation of an inflammatory environment in the synovial fluid, is another key role of TNF-α in the pathogenesis of RA [17].

CHAPTER 4

Vitamin D and Immune System: Implications in Bone Health

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Abstract: Recent studies have identified the involvement of the immune system in several bone complications like osteoporosis, rheumatoid arthritis (RA), periodontitis, osteoarthritis, *etc*. Immune cells have an indispensable role in the regulation of bone metabolism and explicitly influence the differentiation of bone cells by producing various cytokines. Fortunately, recent research has examined different immune-based therapeutics for the prevention of bone diseases in addition to revealing more information about the interaction of the bone and the immune system. Vitamin D maintains bone health by effectively absorbing calcium and thereby promoting bone mineralization. In addition, vitamin D has great immunomodulatory potential and can influence the effect of immune cells and cytokines on the pathogenesis of bone deformities. Therefore, it is plausible to suggest that the detrimental effect of vitamin D deficiency on bone is also linked to the immune system apart from its classic effect on bone mineralization. However, very few studies have enlightened on this aspect of vitamin D-mediated regulation of bone homeostasis which needs to be further unraveled. In the present chapter, we have compiled recent studies highlighting the effect of vitamin D on bone health *via* its effect on the host immune system. Further, we have also highlighted the role of the immune system in the maintenance of skeletal health and then have discussed the effect of vitamin D on various immune cells. In addition, we have reviewed vitamin D-facilitated immune-based approaches for the effective management of various bone pathologies such as osteoporosis, osteoarthritis and rheumatoid arthritis. This information will supposedly help in revealing further mechanistic insights into the immunological regulation of bone health by vitamin D.

Keywords: Vitamin D, Osteoclasts, Osteoblasts, Osteocytes, Immune cells, Cytokines.

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INTRODUCTION

Bone is the metabolically active mineralized connective tissue that provides structural support, helps in muscle attachment for locomotion, safeguards the soft tissue, harbors bone marrow, and is the storehouse of calcium and phosphate [1]. Adult bone is composed of cortical and trabecular bone. Cortical bone is the solid dense compact bone surrounding the bone marrow. Cortical bone has a slow turnover rate and provides resistance to bending [2]. Trabecular bone on the other hand is flexible as it is less dense and has a high turnover rate. It consists of a honeycomb-like network of rods and plates that are interspersed in the bone marrow [2, 3]. Although the ratio of trabecular to cortical bone varies from bone to bone, an adult bone typically has 20% trabecular and 80% cortical bone [3]. Bone remodeling is the process through which bone is continuously modeled during the lifespan of an organism. Bone remodeling replaces the old bone with the new bone and is the result of coordinated action between the primary bone cells *i.e.* osteoclasts, osteoblasts, and osteocytes. Osteoclasts are bone-eating cells that are derived from the myeloid/monocyte hematopoietic lineage. During bone resorption, osteoclasts precursors are recruited towards the bone sites, where they fuse with each other to form the multinucleated osteoclasts that degrade calcified bone matrix by secreting various lytic and acidic enzymes [4]. Two necessary factors that are required for osteoclastogenesis are macrophage colony-stimulating factor (MCSF) and receptor activator of the nuclear factor kappa B ligand (RANKL). Both these factors are required for the expression of primary osteoclast markers such as cathepsin K, tartrate-resistant acid phosphatase (TRAP), calcitonin receptor, and beta 3 integrins. The binding of the RANKL to the RANK receptor on osteoclast precursors induces various changes such as rearrangement of the actin cytoskeleton and formation of tight junctions between the bone surface and basement membrane so that a sealed zone can be created. In this sealed zone (also known as resorption pit or Howship's lacunae), osteoclasts release various lytic enzymes such as TRAP and cathepsin K which lead to bone resorption. Enhanced osteoclastogenesis is the reason behind various bone pathologies such as osteoporosis, RA, *etc*. Osteoblasts on the other hand are bone-forming ones. Osteoblasts arise from the mesenchymal progenitors that also give rise to adipocytes, chondrocytes, and fibroblasts. Osteoblasts secrete the type 1 collagen that makes 90% of the bone matrix and various extracellular proteins such as osteocalcin and alkaline phosphatase (ALP). Osteoblasts also secrete various growth factors such as insulin-like growth factor (IGF), fibroblast growth factor (FGF), transforming growth factor (TGF), and bone morphogenic protein (BMP) [2]. Osteoblasts express the transcription factor RUNX2 and at matured stages both RANKL and osterix. Bone remodeling is the balancing act between the osteoblasts and the osteoclasts by a phenomenon called coupling. Osteoblasts secrete RANKL which promotes osteoclastogenesis. On the other hand

osteoblasts also secrete the osteoprotegerin (OPG) which binds to the RANKL and prevents its binding to the RANK receptor leading to inhibition of osteoclastogenesis. OPG is, therefore, also called as a decoy receptor [5]. The osteoblasts that are entrapped in the bone matrix are called osteocytes. Osteocytes form a network of thin canaliculi that permeates the entire bone matrix and are supposed to provide signals to other osteocytes and osteoblasts. These are also the most abundant and long-lived cells as they can survive for decades in the bone matrix. Osteocytes have a very important role in bone regulation. Osteocytes regulate bone metabolism by regulating both osteoblasts and osteoclasts. Osteocytes produce various signals that induce osteoblastogenesis such as prostaglandin E2, growth factors, glycoproteins, *etc* [6]. Osteocytes negatively regulate the bone by producing the sclerostin protein which acts on the osteoblasts and inhibits bone formation. Sclerostin inhibits the Wnt/B catenin pathway by binding to the low-density lipoprotein receptor-related protein (LRP) 5/6 receptor present on the osteoblast membrane [7]. Osteocytes also secrete RANKL which induces osteoclastogenesis. Proper functioning of our skeletal system requires the critical management of bone remodeling as irregularities in the bone remodeling process result in various skeletal deformities. Several biochemical and mechanical factors such as parathyroid hormone (PTH), estrogen, glucocorticoids, IGF, BMP, TGF-β, *etc*. are involved in the regulation of bone remodeling [8]. Apart from these factors, vitamin D is also a very profound player in bone remodeling. Vitamin D influences the activity of bone cells both directly and indirectly and deficiency of vitamin D leads to skeletal manifestations such as osteoporosis. Recent studies have highlighted the significant role of the immune system in the maintenance of bone metabolism. It is observed that vitamin D has great immunomodulatory potential and prevents various bone pathologies by suppressing the inflammatory environment. However, vitamin D-mediated regulation of bone health by modulating the immune system is not critically revised. Therefore, here we comprehensively discuss the effect of vitamin D on immune system starting with the role of immune system in regulating bone health. Furthermore, we discuss the immunomodulatory potential of vitamin D as a treatment therapy for bone disorders like osteoporosis, RA, and osteoarthritis.

OSTEOIMMUNOLOGY

The term Osteoimmunology was coined for the description of a research field that deals with the interaction between bone and the immune system. Both bone and immune cells share a common origin *i.e.* bone marrow. Immune cells are found to have a very crucial role in regulating bone biology. Findings in the last few years have highlighted the massive breadth of interconnection between bone and immune system and as a result, at present, the role of various immune factors is identified in the maintenance of bone homeostasis. Both innate (monocytes,

CHAPTER 5

Bone Water: Effects of Drugs on Bone Hydration Status

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Abstract: Water is the most crucial nutrient that constitutes roughly 20% of the cortical bone by volume, yet most ignored in health and nutrition areas. Hydration significantly influences the mechanical properties and tissue quality of bone, whereas bone dehydration causes an increase in its elastic modulus. Moreover, the low water content in the trabecular skeleton changes its construction (shrinkage) and leads to a significant alteration in mechanical properties. Numerous internal (a lack of thirst sensation) or external (polypharmacy or chronic consumption of certain drugs) factors cause hypohydration. Unfortunately, frail elderly individuals are more vulnerable to developing dehydration particularly, due to a decrease in the fat-free mass, which contains 73% of total body water. Today, technical advancements have led to an emerging understanding of how bone water changes in various conditions including aging, diabetes, osteoporosis, and osteogenesis imperfecta. Drugs may also change the impression of hypohydration through the increase of water elimination causing diarrhoea, diuresis, or sweat; a decrease in thirst sensation or appetite; or affecting the central thermoregulation mechanism. However, research on the interaction between bone hydration status and drugs/excipients has been insufficient. In the present review, we evaluate studies that focus on the significance of bone hydration and the effects of drugs/excipients on hydration status.

Keywords: Bone water, Total body water, Hypohydration, Bone mineral density.

INTRODUCTION

Age-related diseases are an inevitable feature of human biology, and the increasing prevalence of bone diseases is a reflection of society's age. The loss of bone mass is a consistent outcome of ageing both in men and women. However, loss of bone strength is far more critical than the loss of bone mass in determining the fracture risk [1]. Bone is a nanocomposite polymeric structure having primarily two components hydroxyapatite (mineral phase) and type 1 collagen

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(organic matrix) [2, 3]. The former provides strength and stiffness, whereas the latter influences the toughness of bone. The composite nature of bone cannot be completed without water which is 15-25% by volume, and almost 10% by weight (60% inorganic & 30% organic material), located in different sites, including loosely or tightly bound to the matrix or cortical part [4]. Water is equally significant for the mechanical and structural integrity of both cortical and cancellous bone [5]. Moreover, bone mineral density (BMD) and bone mass are strongly determined by the level of intracellular and extracellular bone water. The dependency of BMD and bone mineral content (BMC) on the level of total body water (TBW), extracellular water (ECW), and intracellular water (ICW) can be seen in transporting fluids in the bone tissue for proper nourishment. The narrow range of TBW is continuously renewed mainly by thirst and hormonal mechanisms and remains in the balance between intake and loss. Any disturbance in the mechanism will lead to dehydration. The dehydration of bone tissue leads to an increase in its hardness, and stiffness, and a decrease in energy and strain at fractures. Several factors such as ageing, sex, drugs, and diseases (diabetes and chronic kidney disease) can negatively impact the water content and lead to bone fragility and fracture. The chronic use of various medications can trigger dehydration or hypohydration by increasing water elimination through sweat, urination, or diarrhoea and also decrease thirst sensation, and altering thermoregulation [6]. Investigation of the bone water content has never been a mainstream subject of analysis. Its examination has been only conducted as a part of a more extensive quantitative analysis of other bone constituents. Therefore, our review will summarize the current understanding of bone water and how the alteration of body water can affect bone hydration and cause mechanical changes. Furthermore, we will evaluate the studies that have talked about the effects of drugs on the hydration status, and how bone water can be therapeutically modulated.

ROLE AND CONTENT OF WATER IN BONE

Bone is a highly heterogeneous composite tissue with every component of utmost importance in maintaining skeletal health. All the components have been studied extensively except water which is the least considered constituent even less than the endosteum, or osseous tissues. In mammalian bone, water comprises 20-25% of TBW. The water in bone exists in two states, bound or mobile/free/pore water. The water that exists in the extracellular space of intra-cortical pores including vascular space and lacuno-canalicular network is called free water. The lacunar-canalicular space contains osteocytes that are estimated at only 12% of the total volume of bone water and provide essential nutrients like glucose to the cells and transport solutes from the lacunar-canalicular system [7]. It means that water not only resides within lacunae, canaliculi, and vascular canals but is also found in

other places like collagen matrix and mineral apatite/extracellular matrix [8]. The water found loosely or tightly bound to the matrix, and other mineralized tissues is called bound water [3]. Both kinds accomplish different roles and their interaction with other components is significant for the mechanical activity of the bone [9].The ratio of bound to free water describes the quality of bone tissue; it can be determined *in vivo* by imaging techniques such as magnetic resonance imaging (MRI). In cancellous bone, the water content is more than that reported in composed or cortical bone. The lower water content in cortical bone may be due to its higher density which can be correlated with its increased mineralization [10]. In a compact bone like femur, the difference in bone density and porosity varies along the length and circumference of the shaft. The porosity increases with age which lets the mobile water fill in pores and decreases the bound water content. It acts as a porosity marker in age-associated bone fragility [11].The water decreases with age due to increased mineralization. But, there is a conflict between studies; some suggest that the water content of cancellous bone decreases from birth to 30 years of age, and remains stagnant thereafter [12], while, another study has demonstrated a steadier loss of water content from birth to death [13]. In addition to that, various pathologies also cause alteration in bone hydration. In osteomalacia, the mineral content of the bone matrix decreases abnormally, and the water content increases correspondingly [12]. Similarly, a significant decrease in bone water has been found in women who had experienced an osteoporotic fracture [14]. Alteration in hydration due to ageing or disease can be a relevant marker in predicting bone diseases, fracture risk, and resistance. It could be better than a bone mineral density (BMD) evaluation. Water along with other components provides essential support like toughness, flexibility, and elasticity to the skeletal system. Hence, loss of water or dehydration affects the viscoelasticity of the tissue which increases tensile strength, stiffness, and hardness and decreases strain and energy to fracture of bone [15]. In ageing and osteoporosis, the amount of water decreases due to increased bone porosity. Thus, loss of toughness due to the less amount of water bound to collagen or increased collagen cross-links that displace water in the collagen matrix. It results in bone fragility [9]. Similarly, hydroxyapatite increases due to the mineralization of ageing bone till the age of 60 years which causes bone stiffness [16]. As the patient gets old, bones get stiffer due to increasing mineral content, and decreasing quantity of water resulting in brittle bone due to bone mineralization which is fracture-prone [16]. Another study has used solid-state NMR to elaborate on the role of water in bone and its association with bone constituents. Water forms structural support to the tissue by forming H-bonds support between the neighbouring ions [17]. The presence of crystal-bound water fills the vacancies and prevents the collapse of these crystallites. Furthermore, the water spread over the surface of mineral crystals helps in coupling the mineral phase with collagen phases, thus, serving to

CHAPTER 6

Dietary Patterns and Rheumatoid Arthritis

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Abstract: Rheumatoid arthritis (RA) is a systemic autoimmune inflammatory disease that impairs patients' capacity to engage in everyday activities and deteriorates their quality of life. The disease develops in genetically vulnerable individuals *via* an autoimmune inflammatory process triggered by environmental stimuli. Diet and nutrition are potential environmental variables influencing the start and progression of the disease. Traditionally, nutrition and disease research has examined the relationships between individual nutrients, foods, or dietary groupings and risk factors with health outcomes. By examining food consumption in terms of dietary patterns, it is possible to gain complete knowledge of the combined effects of nutrients and foods on chronic illnesses. The Mediterranean, DASH, and vegetarian diets are preventive dietary patterns, whereas the Western diet stimulates RA activity.

Keywords: Rheumatoid arthritis, Dietary pattern, Mediterranean diet, DASH diet, Vegetarian diet, Western diet, Inflammation, Disease activity, Joints, Nutrients.

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic autoimmune inflammatory disease that affects joints predominantly, with an approximate worldwide prevalence of 1% [1]. It has particular symptoms characterized by persistent inflammation that originates in the synovial membrane and leads to joint cartilage damage. It can lead to painful joint swelling, bone degradation, and the beginning of major bodily function impairments at an early age. RA has a negative impact on a patient's ability to do normal daily activities and can impair quality of life. Also, it entails a high economic burden on people and societies [2].

The disease develops in genetically susceptible individuals through an autoimmune inflammatory process caused by environmental factors [3]. Environmental factors such as smoking, air pollution, dust, and infections play an

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important role in the etiology of the disease. Diet and nutrients are possible environmental factors impacting the onset and development of disease [4]. Accordingly, dietary intervention is commonly used to manage and reduce the symptoms of RA through multiple mechanisms, such as reducing inflammation, increasing antioxidant levels, modifying lipid profiles, and possibly altering the gut microflora [5].

Traditionally, studies on nutrition and diseases have investigated the associations between specific nutrients, foods, or food groups with risk factors and health outcomes. However, this approach has some limitations; the most important is that nutrients or food groups are not though diet is particular to the Mediterranean basinonsumed in isolation. It must be noted that "we don't eat nutrients, we eat foods," and that, in reality, we consume foods in specific patterns [6, 7]. In response to these limitations, a more comprehensive understanding of the combined impacts of nutrients and foods on chronic diseases may be obtained by exploring food intake in terms of dietary patterns. It is more applicable for clinicians and patients to focus on dietary patterns rather than particular nutrients in order to make beneficial dietary modifications to manage their disease [2, 8]. Regarding an individual's entire diet, a healthy dietary pattern provides nutritional adequacy, minimizes the risk of chronic diet-related diseases, and improves overall health [9]. Accordingly, in this chapter, we explore major dietary patterns that affect RA symptoms and development.

MEDITERRANEAN DIET

The Mediterranean diet is a plant-based dietary pattern consumed by people of countries bordering the Mediterranean Sea, particularly in Greece, southern Italy, and southern Europe (Fig. **1**). It is recognized as one of the world's healthiest dietary patterns, particularly for its role in preventing chronic diseases.

The Mediterranean diet is characterized by the following:

1. Daily consumption of non-refined cereals and other products (such as whole wheat bread, pasta, and brown rice), fresh fruits, vegetables, nuts, legumes and low-fat dairy products and limit refined sugars.
2. Frequent consumption of olive oil as the primary source of fat.
3. Moderate consumption of fish, poultry, potatoes, eggs, and sweets (It is advised that fish and seafood be consumed at least twice a week).
4. Monthly consumption of red meat.
5. Moderate intake of alcohol, preferably red wine, with meals.
6. Regular physical activity.

Although diet is particular to the Mediterranean basin, its principles are easily adaptable to accommodate foods and recipes from different cultures across the world [10, 11]. The scientific and public interest in the Mediterranean diet as a healthy and recommended eating pattern for the prevention and treatment of various health issues, including cardiovascular diseases, diabetes, arthritis, cancer, and obstructive sleep apnea, has increased considerably in recent years [12, 13].

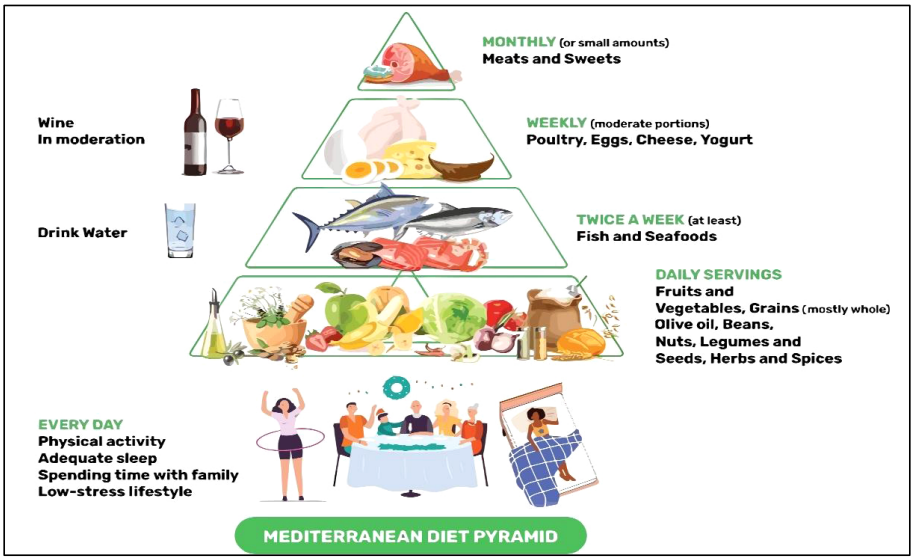

Fig. (1). The Mediterranean diet Pyramid.

However, there are contradictory studies regarding the effectiveness of the Mediterranean diet for RA. Sköldstam et al. found that the Mediterranean diet reduces disease activity in patients with stable and moderately active RA [14]. A significant reduction in disease activity score (DAS28) and overall health perception has been reported, as measured by the health assessment questionnaire (HAQ). Using the Short Form-36 (SF-36) questionnaire, increases in the individuals' quality of life were also seen. In another study, the intervention group showed significant improvements in terms of the disease's clinical characteristics, pain, morning stiffness, and health assessment perception after six months [15]. A population-based case-control study has demonstrated an inverse relationship between the Mediterranean diet and the risk of RA, but only in males with seropositive RA [16]. Another prospective study, investigated the association between adherence to the Mediterranean diet and the risk of getting RA in women in the United States [17]. The Mediterranean diet was evaluated using the Alternative Mediterranean Diet Index (aMed), which was calculated using the frequency of intake of nine food groups: whole grains, legumes, fruits, vegetables,

CHAPTER 7

Self-perceived Quality of Life in South Asian and British White Rheumatoid Arthritis Patients in the East Midlands, UK

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Abstract: It has been suggested that South Asian patients with RA report increased levels of pain and demonstrated increased disease severity as compared to the British *white* population. This study assesses the self-perceived quality of life in South Asian RA patients compared to White British RA patients. 131 South Asian (SA) and 134 British White (BW) RA patients from the East Midlands participated in the study as a part of ongoing studies on RA pathogenesis by completing the qualitative lifestyle questionnaire. The SA patients developed RA significantly earlier than BW patients (χ^2 = 21.01, P = 0.001, df = 5). Compared to the BW, a majority of SA perceived the disease to be severe (χ^2 = 8.57, P < 0.05, df = 3). They also reported higher pain (χ^2 = 26.12, P < 0.05, df = 3), reduced mobility (χ^2 = 17.57, P < 0.004, df = 5) and reduced physical activity performed (χ^2 = 17.94, P < 0.0005, df = 3). Reduced mobility and a decrease in physical activity may be associated with a higher perception of RA-related pain among South Asians. This may have important public health implications in terms of disease progression and treatment modalities.

Keywords: QoL, South Asian, British White, Rheumatoid Arthritis.

INTRODUCTION

Rheumatoid Arthritis (RA) is a chronic, multi-system disease with a considerable impact on the lives of individuals and their families. RA affects approximately 1% of the adult population. The East Midlands of the UK is an area with a substantial South Asian population. To optimise care, it is important to gather specific infor-

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mation about this group of patients. The government initiative to provide equality in healthcare because of the Race Relations Amendment Act 2000 [1] and the King's Fund recommendation [2] suggests that ethnically specific data needs to be collected across the NHS to optimise healthcare. This would include obtaining and responding effectively to the patients 'raw feelings' (patients' perception of the disease treatment following the confirmatory diagnosis of RA). Quality of life (QoL) measures are equally important to measure in chronic disease management and this may reflect on patient satisfaction. In other words, if patients perceive that their quality of life is at a reasonable level then it may follow that they have greater satisfaction and (possibly confidence) in their current treatment. The beneficial effects on their health may reflect this, in the longer term.

Both environmental and genetic factors have been documented to play a significant role in the pathogenesis of RA. However, measures of disease activity and disease damage are insufficient to fully assess the impact of RA on an individual. This aspect is also important to clinicians in assessing the benefits of prescribed medications. There are only a few studies on patients from South Asia (India, Sri Lanka and Pakistan) with RA on this aspect and no comparative studies have been published [3]. These studies have used health-related quality of life (HRQoL) questionnaires reflecting patients' subjective evaluation of the effects of disease on their physical, psychological and social functioning. Studies on RA QOL have clearly documented that RA has a profound effect on the functioning and well-being of patients [3]. While HRQOL and other QoL instruments are useful tools, all have limitations. These questionnaires tend to be detailed, take a long time to complete, and have limited availability of validated translated versions. The translated questionnaires often do not convey the correct interpretation and have poorly translated terminologies that ethnic minorities may have difficulties comprehending, resulting in problems in the completion of the questionnaires. The current validated questionnaires often fail to assess 'raw feelings' [4], in relation to out-patient complaints, which may prove to be a more sensitive measure for what needs to be altered (if at all) within clinical practice. In this study, we have assessed patients' perception of quality of life (QoL) amongst hospital-referred South Asian (SA) and British White (BW) RA patients from the East Midlands by means of a questionnaire. We hypothesized that both groups would have similar perceptions of QoL as all participants are from the same geographical area, share similar environmental features, and have similar accessibility to health services. In this questionnaire, we specifically focused on the perception of pain and severity, disability, and medications.

METHODS

Rheumatoid factor-positive RA patients between the age of 20 and 75 years participated in the QoL assessment; all fulfilled the ACR 1987 criteria for RA [5]. A self-administered questionnaire written in the English language was used in the study. Complete access to appropriate interpretation/translation facility was available to all participants. The questionnaire was piloted to assess the suitability and understanding of questions among participants, some questions were reworded to avoid any confusion. The questionnaire consisted of questions related to personal information (age, gender, marital status, ethnicity, family status, occupation, diet, cigarette and alcohol consumption, exercise, duration of disease, self-perceived severity of disease and pain, and medications). Patients were requested to indicate mild, moderate or severe state of daily pain and RA status, mobility and amount of daily exercise performed in hours. The effect of other 'raw feelings' on the scoring was monitored by providing a facility in the questionnaire to comment on any other aspects of the disease. The progression of RA in the two ethnic groups was calculated by deducting the age of the patient at the time of answering the questionnaire from the confirmed onset of the disease at the RA clinic.

About 10% of participants were asked to complete the questionnaire on more than one occasion to ascertain whether they provided the same responses and a degree of internal validity in responses.

The study received Loughborough University Ethics Committee and NHS approval and all subjects gave written informed consent. SPSS (Version 15.0.1) was used for statistical analysis.

RESULTS

131 South Asian (M = 28, F = 103) and 134 British White (M = 36, F = 98) participants successfully completed the questionnaires. Most South Asian participants were migrants mainly from India and composed of Gujarati and Punjabi groups. Some Gujarati participants migrated to the UK from East Africa (Kenya, Uganda and Tanzania). Britsh White participants were natives from the East Midlands of the UK.

Age and Gender Distribution

The mean age of SA patients was 52.5 years (Standard deviation (S.D.) of 10.3 years, n = 131) and BW was 58.9 years (S.D. 10.3 years, n = 134). The difference was statistically significant ($t = 5.10$, $P<0.0001$). Age distribution (Fig. **1**) showed that there were more SA-RA patients (41%) in the age range of 31 to 50 years as

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