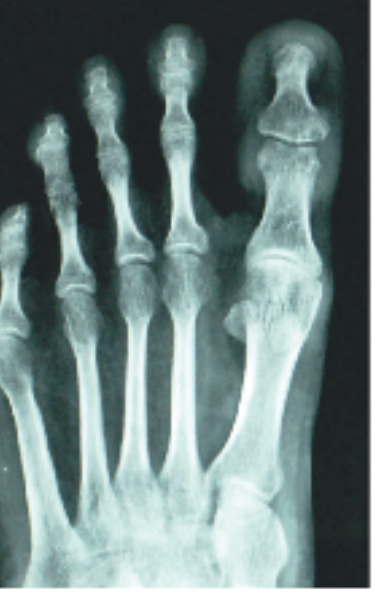

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CONTENTS

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NIC PHARMA

Developing a rheumatology team to meet a growing need in Africa: let's not forget to feed the cow

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In many African countries the burden of preventable communicable diseases such as HIV/AIDS, lower respiratory infections, malaria and diarrhoeal diseases is overwhelming[1]. It therefore is no surprise that moving Rheumatic and Musculoskeletal Disease (RMDs) up the public health agenda is difficult. The health needs of the African continent are complex and diverse, but priority setting is challenging in an environment hampered by financial constraints and limited epidemiological data. This can be further complicated by lack of resources and donor-dependent economies[2].

Taking these factors into account, it is not an easy task to engage public health systems across Africa to include Rheumatic and Musculoskeletal Disease (RMDs) on their list of health priorities. Yet, the burden of RMDs has shown a marked increase and now has a truly global impact. Although the epidemiology data in Africa are limited, RMDs have the fourth largest impact on the health of the world's population, when considering both death and disability (DALYs), and are the second most common cause of disability worldwide when measured by years lived with disability (YLDs)[3,4]. As the world population ages and obesity is on the rise, this burden is set to increase further.

Onset of RMDs, however, often occurs in the working age population, so failing to effectively treat RMDs has a socioeconomic impact both at the individual and societal level. Losing employment through illness has a double effect on a family, who not only lose income but need to increase their expenditure to meet associated healthcare costs.

Data from the UK indicates that as many as a third of patients with Rheumatoid Arthritis (RA) become unemployed within the first five years of their diagnosis, with rates highest in those with higher level of physical disability or manual jobs[5]. The economic impact of losing experienced workers from RMDs should not be underestimated in Africa, where there are higher rates both of manual work and disability[6]. Failing to effectively treat RMDs now, or to develop a health workforce capable of dealing with a likely future increase in the number of people with RMDs, will further impede Africa's economic development over the coming years.

Although some of these challenges can be met by increasing health spending, where this is not possible, much can also be achieved by using the scarce health resources in new ways[2].

The growing burden of RMDs is juxtaposed with our increasing effectiveness in treating these conditions: we're now better able to influence patient outcomes than ever before. For example in Rheumatoid Arthritis (RA), treatment is now aimed at remission[7], once considered unachievable. Progress has been most pronounced in inflammatory arthritis and stems from the paradigm shift towards identifying patients early, initiating effective therapies within three months of symptom onset, regular disease assessment and maintaining tight disease control. Whilst few would disagree with the benefits of the current paradigm, there is a clear challenge for under-resourced health systems to deliver this model of care on a population level[6]. Indeed the challenge of finite resources, greater patient need, and rising treatment costs is one that faces health systems across the world. Yet, this is a challenge that we must all meet if we are to improve the quality of life for our patients and minimise the economic burden of RMDs.

Within the UK health system, care is free at the point of delivery but health spending; the healthcare workforce; and the healthcare system's architecture have struggled to meet the needs of a modern population. This problem is not new, and in the 1990s a growing shortage of doctors led to a corresponding gap in service delivery. This crisis signalled the start of an ongoing journey. The roles of nurses and Allied Health Professionals (AHPs) had to expand to fill some of these gaps through new extended scope roles, to deliver tasks that were traditionally the preserve of doctors. This change did not occur overnight, and much work was required to change legislative frameworks to allow such roles to develop safely and effectively. Nurses were the first to

pioneer advanced roles[8] and now highly trained nurse specialists have a range of skills such as joint injections and prescription rights[8,9]. As care for people with RMDs evolves so do these roles and there is now evidence from high quality multicentre randomised controlled trials which demonstrates that nurse led care is cost effective, safe and patients report higher levels of satisfaction than they do in traditional medically led models of care[10]. Such has been the success of nurse specialists, that they are now an essential part of every rheumatology service in the UK and elsewhere in Europe[11-14], where they work collaboratively with rheumatologists, within the framework of a multidisciplinary team, rather than in competition.

In Europe, much has been achieved by offering early access, regular disease assessment and patient education using a strong team approach, with nurses and AHPs advancing their skills to enhance the care provided by the medical team. This allowed for a larger volume of patients to be seen and managed safely. This team approach has served to optimise the role of the rheumatologist and enable the services to deliver more cost effective care. For example, some clinics now use specialist nurses to coordinate care and undertake routine patient monitoring, freeing the rheumatologist's time to deal with new and more complex cases. Such an approach would represent a logical progression in Africa where non-physician providers such as medical assistants and assistant medical officers have been used effectively for many years within their healthcare systems with great effect[15].

Advanced nursing practice is established in the UK but in different stages of development across Europe[14]. In other parts of the world such as in Asia, nurses are now starting this journey and have recently endorsed rheumatology nurses as a specialist area of practice with appropriate training[16]. Each country must develop a solution to meet the specific challenges it faces utilising the differing resources at it's disposal. By learning from the reality of patients' experiences of seeking health, healthcare communities will learn where we can most effectively optimise care and reduce costs. Although a 'one size fits all' approach is unlikely to work, our experience has shown there are some common obstacles to overcome when starting this journey, and indeed many of these reoccur over time as administrations change. Training nurse and AHP workforces to meet this clinical need requires changes in legislation, investment, and a cultural change from all within healthcare so that clinical need and patients outcomes and safety come before traditional professional boundaries and personal interests.

Developing services in such a way does not happen overnight and needs to be managed in a stepwise approach and although individuals are key to the process, it cannot be achieved alone. National and continental bodies are vital with regards to the political agenda but individuals have a responsibility to foster a culture where development of nurses and AHPs is welcomed and encouraged in order to improve care. The wider healthcare workforce should be valued and developed in order to ensure sustainable health services. Similarly, individual nurses and AHPs have a responsibility to take ownership of their own development and maximise opportunities when they present. The global rheumatology community should work collaboratively to support each other in developing care for people with RMDs. One example of this has recently been afforded through the British Society of Rheumatology (BSR) who for the first time, provided two bursaries through the African League Against Rheumatism. These bursaries provide funding for one rheumatologist (Dr Joan Delour. The first recipients of the bursaries were Dr Segun Akintayo Oguntona and Mrs Irene Oduenyi) and one nurse (The BSR Nursing Travel Bursary) to attend the annual BSR conference and to then spend time in a leading rheumatology unit. The annual conference not only contains highlights from world leading researchers, practical sessions, and a range of networking opportunities but also enables clinicians and researchers to discuss challenges in delivering care as well as sharing ideas on implementing the latest research findings. Sharing such opportunities internationally provides a vital link between the United Kingdom and Africa and it is hoped that the bursaries may make some small step towards stronger collaboration.

Addressing the growing burden of RMDs is a challenge that Africa must embrace and overcome in the coming years. As the saying goes: 'he who keeps a healthy cow will have plenty of milk', training the workforce is not a waste of resources. Some countries have already started down this journey and found great benefit in growing the nursing and AHP specialist workforce. This journey is achievable and likely to be rewarding. Although it may take many years, small steps are needed at the start. Could the new bursaries be the first step of your journey?

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Insights into methotrexate in rheumatoid arthritis: a clinical review

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Abstract

Objective: To review the efficacy and safety profile of methotrexate in rheumatoid arthritis.
Data source: Published original research work and reviews were searched in English related to efficacy and safety profile of methotrexate in rheumatoid arthritis.
Study design: Only articles that emphasis on efficacy and safety profile of methotrexate in rheumatoid arthritis.
Data extraction: Online and library searches done.
Data synthesis: Data added and summarized.
Conclusion: Methotrexate (MTX) has been the mainstay of treatment of patients with Rheumatoid Arthritis (RA). It has been used for over 50 years as the backbone in the treatment in a number of rheumatic diseases and thus it remains a gold standard of therapy for RA. Clinical trial results indicate that weekly low dose MTX is generally safe and effective in the treatment of RA. Factors that favour a good response to MTX are male gender, non-smoking, early disease stage, absence of previous DMARD use, lower baseline disease activity, concomitant corticosteroids, inflammatory biomarkers (TNF-α levels, ESR, CRP) and HLA-DRB1 shared epitope (SE)-negativity. Folate supplementation has been shown to reduce the risk of adverse events.

Key words: Methotrexate, Rheumatoid arthritis, Efficacy, Safety profile

Introduction

Methotrexate was first used for the treatment of rheumatoid arthritis in 1951[1]. It emerged at the same time as glucocorticoids. It received little attention in the therapy of rheumatic diseases until retrospective reports appeared about 30 years later[2,3]. The initial short term studies in the mid-1980s demonstrated that it was more potent, efficacious and superior to placebo in patients with chronic severe RA. Long-term open prospective studies have since showed that the response is sustained and that toxicity is manageable. These insights have led to the evolution of methotrexate into its present status as the main stay of treatment of patients with RA. However, there is a large variability in the medical practice regarding the use of methotrexate for RA. The variability occurs mainly with regards to the starting dose, adjusting dosages, routes of administration and concomitant use of folic or folinic acid. The purpose of this article is to provide guidance on the use of methotrexate for the treatment of RA.

Mechanism of action

Methotrexate was introduced for the therapy of rheumatoid arthritis without any clear understanding of its mechanism of action. With methotrexate, studies are even more difficult to interpret because the effects of methotrexate are observed over weeks to months in patients. Another caveat is that studies in animals may be misleading because the doses of the drug used are not similar to those used in patients. It's important to note that the methotrexate effect in animals is seen over a shorter duration of time as compared to humans[4]. Despite these, there are a number of postulated mechanisms of action.

The first hypothesis, based on methotrexate's known anti-folate properties. Methotrexate is a structural analogue of folic acid that competitively inhibits the binding of dihydrofolic acid to the enzyme dihydrofolate reductase. Dihydrofolate reductase is enzyme responsible for reducing dihydrofolic acid to the active metabolite, folinic acid. Therefore, methotrexate decreases the amount of intracellular folinic acid available and affects the intra-cellular folinic acid dependent metabolic pathways. These pathways include purine and pyrimidine metabolism, as well as amino acid and polyamine synthesis. Its postulated by inhibiting these methylated reactions it inhibits proliferation of the pro-inflammatory cells and cytokines responsible for synovial inflammation in RA[5,6].

Other mechanism of action includes increasing T cell apoptosis and release of endogenous anti-inflammatory adenosine. It also alters the expression of cellular adhesion molecules thus reducing in expression of cellular adhesion molecules and anti-angiogenesis effects via indirect mechanisms such as disruption of macrophage interaction[7,8].

Efficacy for rheumatoid arthritis

Methotrexate can be given by oral, intramuscular, and subcutaneous routes. The oral route has a variable absorption and has less serum levels when compared to parenteral administration [9, 10]. This may have therapeutic implications, as some patients may seem to respond better to parenteral therapy, presumably because more drugs reaches the circulation especially when higher doses within the therapeutic range are used. The liquid MTX formulation (prepared for parenteral use) may be consumed orally by mixing it with juice; this preparation is cheaper than tablets and may be used if expense is a serious issue and if the patient can be relied upon to measure the precise volume of drug. It is not recommended for patients with decreased finger dexterity, limited vision, or impaired cognition. Research has shown that better disease activity scores can be attained from switching to parenteral administration with patients on maximally tolerated oral doses of MTX. Toxicity has been noted to be higher in the parental group[11,12].

Its use in rheumatoid arthritis is well known. Apart from improving disease activity scores, it also has benefits of reducing mortality, improving quality of life and reducing radiographic joint damage[13,14]. With the introduction of biologics, data from Kleinert's study, Gruppo Italiano Studio Early Arthritis (GISEA), British Society for Rheumatology Biologics Register (BSRBR), and Research in Active Rheumatoid Arthritis (ReAct) still show that methotrexate is still the anchor for rheumatoid arthritis management[15-17]. Despite its popularity in rheumatoid arthritis, the dose and route of administration has been varied. To determine the best dose and route of administration, we looked into data from previous studies.

The starting dose has been an area of contention. Furst *et al*[18] compared starting doses of 5-10mg weekly, 12.5-20mg weekly and 25-35mg weekly vs placebo in RA patients who had the disease for a long duration and had failed other Disease Modifying Antirheumatic Drugs (DMARDs). The best response in terms of tender joint counts, pain and global status versus the placebo was noted in the 12.5-20mg group. The 25-35mg group had the highest adverse events as measured by gastrointestinal and mucocutaneous toxicities.

In early RA DMARD naïve patients, Verstappen *et al*[19] looked at two groups. First group started at 7.5mg per week and increased it per month by 5mg up to a maximum of 25mg weekly. The second group had a slower increment of 5mg every 3 months to a mean of 18mg weekly. Patients in the group with the fast increment achieved better disease control as measured using tender and swollen joint counts, pain and global status. Interestingly both groups had similar records of adverse events. The general recommendations are start patients on 15 mg weekly orally, escalating 5 mg per month to 25-30 mg weekly as tolerated depending on disease activity, size, and age of the patient, the presence of comorbidities, and renal function. If response is inadequate, one should consider switching to SC where available[20].

The response to any DMARDs be it synthetic or biologic varies from one RA patient to another. This is due to the unique and complex pathogenesis of RA which causes varied clinical presentation. The next frontier in management is being able to predict the responders to drugs used in RA treatment. A novel biomarker of response has been methotrexate polyglutamate. These are the active MTX metabolites that produce the anti-inflammatory effects and their levels have been found to correlate to disease activity[21,22]. Higher levels are associated with good responses, while lower levels might indicate the need for either more MTX, or the possibilities of poor adherence to the treatment regimen or poor absorption of the dose inhibit enzymes of folate metabolism[21,22]. Data is still limited and more research is needed before this can be applied to routine clinical use. The known clinical and biological factors that predict good response to MTX are male gender, non-smoking, early disease stage, absence of previous DMARD use, lower baseline disease activity, concomitant corticosteroids, inflammatory biomarkers (TNF-α levels, ESR, CRP) and HLA-DRB1 shared epitope (SE)-negativity[22-23].

Safety profile

MTX use has been associated with a variety of adverse effects. The range of severity is influenced by the MTX dose and treatment regimen. The major side effects are reviewed here.

Common minor adverse events

Gastrointestinal

The common side effects include nausea, loose stools and stomatitis. Stomatitis can occur at any dose of MTX but is more likely to be seen at higher doses. These are mainly due to sub-optimal supplementation of folic acid. Patients with mild to moderate stomatitis, one can gradually increase the folic acid dose from 1 mg daily increments up to a maximum of 5 mg until the toxicity is controlled. Patients presenting with severe oral ulcers may require both a lowering of the MTX dose and an increase of folic acid[24].

Neurotoxicity

Manifestations include severe headaches, fatigue, and problems in concentrating which may require reducing the MTX dose or discontinuation in some patients. The exact mechanism is still unclear. Some have suggested it may be related to the accumulation of adenosine due to the inhibition of purine synthesis[25].

Fever

MTX can induce fever either directly or indirectly through infections. Infections are rare but commonly occur with co-administration of glucocorticoids, azathioprine and tumour necrosis factor inhibitors. Pneumocystis jiroveci, herpes zoster and fungi can occur. Infections are a common cause of drug withdrawal among those administered MTX for prolonged periods[26].

Potential severe adverse effects

Hepatotoxicity

Low dose methotrexate can have adverse effects on the liver. These include reversible transaminase elevation (most common), liver fibrosis and liver cirrhosis (rare). Risk factors include alcohol and preexisting liver disease. Other risk factors for elevated transaminases include obesity, untreated high cholesterol, Aspartate Transaminase (AST) or Alanine Transaminase (ALT) elevations above the upper limit of normal at baseline (before starting MTX) use of a biologic agent in addition to the MTX, and lack of folic acid supplementation[27]. Some authors suggest that folate supplementation may help prevent MTX induced hepatotoxicity. Methotrexate depletes the folate hepatic stores and supplementation either folic acid 1 mg per day or folinic acid 2.5 mg per week is associated with a reduced incidence of serum transaminase elevation[28]. However, more research is needed to establish the relationship between folate depletion and hepatic toxicity.

Data from the CORRONA database that 1953 RA and 151 psoriatic arthritis patients, showed there was an increased risk of transaminase elevations with a combination of MTX and leflunomide compared with either drug used alone[29]. The overall incidence of elevations in aminotransferase enzymes in patients with RA receiving MTX, leflunomide, MTX plus leflunomide, and neither was 22, 17, 31, and 14%, respectively. Elevations > 2 x ULN occurred in 1-2% of patients on MTX or LEF monotherapy compared to 5% with the combination. After multivariable adjustment and compared with either monotherapy, combination MTX + LEF was associated with greater risk according to MTX dose used as part of the combination.

Data from the SMILE cohort (Safety of Methotrexate and Leflunomide in RA trial) over a period of 12 months examined transaminase abnormalities in 2975 patients. The overall incidence of elevations in aminotransferase enzymes in patients receiving MTX (52.2%), Leflunomide (7.3%), MTX plus Leflunomide (13.9%), and neither (26.6%) was 12, 16, 19, and 14%, respectively[30]. No reports of liver fibrosis or cirrhosis were recorded. Only a small number of patients had to stop taking MTX and/or LEF cessation due to AEs.

The above results are reassuring that rarely do serious liver abnormalities occur in patients using low dose. Other novel non-invasive methods are under investigation to detect hepatic injury and fibrosis. As an example, ultrasound-based transient elastography has been used in preliminary studies of patients receiving MTX for inflammatory arthritis, psoriasis, and gastroenterologic disorders but has not been evaluated for its utility in monitoring patients with RA receiving MTX in clinical practice[31].

Recommendations dictate that, in patients on a stable dose of MTX, monitoring at an interval of every 8 to 12 weeks is appropriate after three months of therapy and monitoring every 12 weeks can be performed beyond six months of therapy. Liver biopsies are no longer recommended on all patients on MTX but only done based upon the presence of risk factors for hepatotoxicity[32]. A pre-treatment biopsy is considered only for patients with a history of excessive prior alcohol consumption, persistently abnormal baseline AST values, or chronic hepatitis B or C infection [32].

Pulmonary abnormalities

The incidence of pulmonary abnormalities remains low. A systematic review on 21 prospective studies reported that only 15 (0.43%) out of 3463 RA patients on MTX treatment on follow up for 36.5 months developed MTX pneumonitis[33]. The authors concluded MTX pneumonitis be considered as an acute hypersensitivity reaction, occurs early in the course of MTX, thus it does not seem to be a problem of long-term treatment by MTX. Factors that have been associated with MTX- induced lung injury include higher weekly doses of methotrexate, preexisting interstitial lung diseases, abnormal pulmonary function tests prior to therapy, decreased elimination of methotrexate (e.g., as seen in renal insufficiency or with the presence of third-space fluid collections such as ascites), hypoalbuminemia (either before or during therapy), diabetes mellitus previous use of disease-modifying antirheumatic drugs, cigarette smoking, and low body weight[34]. The mechanism by which some of these factors may confer excess risk is unclear. There is data supporting hyperinsulinemia, which may occur with treatment for diabetes mellitus, is associated with increased polyglutamation of methotrexate. The previous use of disease-modifying antirheumatic drugs may be a marker for more severe rheumatoid arthritis, and hypoalbuminemia could potentially result in a lower degree of protein binding and higher free levels of methotrexate[34-36]. The acute presentation typically includes fever, chills, malaise, nonproductive cough, dyspnea, and chest pain; the subacute presentation is characterized by a more insidious onset of dyspnea, cough, and fever. The majority of patients who develop methotrexate pulmonary toxicity do so within the first year of therapy[33].

Myelosuppression

This is commonly seen when using MTX in high doses. With low dose MTX therapy, anaemia, neutropenia and lymphopenia are the commonest abnormalities encountered in RA. Thrombocytopenia is rare now that Felty's syndrome isn't common[37]. A more serious problem is pancytopenia which has been associated with elderly, those with concomitant use of dihydrofolate reductase inhibitors, and patients with renal impairment[38].

In a study by Bird *et al*[30] where they reported a lower incidence of neutropenia rate of neutropenia was higher in patients not taking MTX, than those taking MTX as monotherapy. They defined neutropenia as neutrophil count of < 2.0 x 10^9/L and found that 2.3% of the MTX monotherapy group, 5.5% of the LEF monotherapy group, 3.9% of the MTX/LEF combination group and 4.2% of the group taking neither drug. They however concluded that these values did not correspond to an increased incidence of infection.

Guidelines recommend that a routine peripheral complete blood count should be performed every four weeks during the first three months of therapy, every 8 to 12 weeks from three to six months, and every 8 to 12 weeks thereafter, depending upon the nature and/or severity of abnormalities noted during monitoring[32].

Risk of malignancy

The incidence of cancer and mortality by cancer are slightly higher in RA cohorts as compared to the general population[39,40]. Hematopoietic and lung cancers make up the majority of numbers[39]. Rarely, lymphoproliferative "malignancies" may develop after long-term therapy but regress spontaneously after MTX is withdrawn. They are usually of B-cell origin and some are associated with latent Epstein Barr virus infection[41]. Chemotherapy should be withheld until MTX has been stopped, since some of these tumours regress within four weeks after MTX has been discontinued. Continued vigilance is necessary in those who regress, since relapse has been reported[42,43]. Drug therapy does not confer a direct risk to developing cancer. A Canadian study of 23810 patients followed up between 1980 - 2003 reported 619 haematological malignancies (lymphoma in 346, leukaemia in 178 and myeloma in 95). Analysis performed to assess the effect of DMARD therapy showed that the unadjusted ratios for haematologic malignancy after drug exposures were: MTX 1.18 (95% CI 0.99-1.40), azathioprine 1.44 (95% CI 1.01-2.03) and cyclophosphamide 2.21 (95% CI, 1.52-3.20)[44]. There is an increased risk for malignancy, but the above data reassures that the numbers are still low.

Conclusion

Methotrexate is still the anchor for rheumatoid arthritis management. Clinical trial results indicate that weekly low dose MTX is generally safe and effective in the treatment of RA. Factors predictors of good response to MTX are male gender, non-smoking, early disease stage, absence of previous DMARD use, lower baseline disease activity, concomitant corticosteroids, inflammatory biomarkers (TNF-α levels, ESR, CRP) and HLA-DRB1 shared epitope (SE)-negativity. It has advantages in long term treatment due to cost and is generally well tolerated due to its favourable adverse effect profile. The most commonly observed side effects of MTX at doses typically used for the treatment of RA are rarely life-threatening. Folate supplementation has been shown to lower the risk of adverse events. Physicians need to know the risks associated with its use and monitor accordingly.

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Research article

Bone mineral density abnormalities in HIV infected patients and HIV negative respondents at Mbagathi Hospital using calcaneal quantitative ultrasound

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Background: Osteoporosis is a systemic skeletal disorder characterized by low bone mass and micro-architectural deterioration of bone tissue, with a consequent increase in bone fragility and fracture. Use of Highly Active Anti-Retroviral Therapy (HAART) has been associated with prolonged survival and consequently with an increase in the prevalence of decreased bone mineral density. Quantitative Ultrasound (QUS) is gaining popularity as an appropriate tool for determination of bone mineral density profiles in resource- poor settings.

Objectives: To determine and compare the difference in the prevalence of Bone Mineral Density (BMD) abnormalities using quantitative calcaneal ultrasound between HIV infected patients on a TDF based first-line regime for at least one year, HAART-naive HIV positive patients in Mbagathi Comprehensive Care Clinic (CCC) and a HIV negative control group seen at the Mbagathi Voluntary Counselling and Testing Centre (VCT). To describe the occurrence of traditional risk factors associated with decreased BMD in the above populations (oral corticosteroid use, smoking, alcohol, previous bone fracture, body mass index and physical inactivity).

Methods: This was a cross-sectional comparative group descriptive study of HIV positive adult patients on TDF based first-line regime (exposed), HIV positive HAART- naive adult patients (unexposed) and HIV negative adult group (control) at Mbagathi Hospital. Random sampling was used to recruit 315 participants (105 in each arm). An interviewer administered questionnaire was used to document risk factors for low BMD. Quantitative ultrasound bone mineral density was done using a heel ultrasonic gel- coupled QUS system, the Sunlight Mini Omni (Beam Med Ltd, Israel).

Results: The prevalence of osteoporosis among HIV positive respondents on HAART was significantly higher (58.1%) compared to HIV positive respondents not on HAART (32.6%) (Z-test p-value = 0.001) and HIV negative respondents (9.3%) (Z-test p-value = 0.001). Older patients had lower levels of BMD (i.e. more negative BMD. p-value = 0.032). HIV positive respondents on HAART had lower BMI than HAART naïve and HIV negative individuals (23.6%, 24.8% and 26.1% respectively). There was a significant positive correlation between T-score and BMI (p-value 0.043). There was no significant correlation between T-score and the other traditional risk factors (oral corticosteroid use, smoking, alcohol use, history of bone fractures and physical activity).

Conclusions: Use of TDF based HAART regimes is associated with higher rates of osteoporosis compared to HAART naïve and HIV negative populations which may be partly mediated by lower Body Mass Index (BMI).

Introduction

Human Immune-Deficiency Virus (HIV) infection is one of the heaviest infectious disease burdens afflicting sub-Saharan countries. Kenya has the fourth-largest HIV epidemic in the world and in 2012, an estimated 1.6 million people were living with HIV, and roughly 57,000 people died from AIDS-related illnesses[1,2]. Since 2008, the expansion of ART services throughout the national healthcare system had increased the number of adults on treatment from 64% to 80% in 2013[3].

Use of Highly Active Anti-retroviral Therapy (HAART) has been associated with viral suppression and improved patient survival. With prolonged life, the prevalence of osteoporosis and osteopenia increases due to differential bone remodeling associated with aging[4,5]. HIV causes osteopenia through cytokine and inflammatory- mediated pathways[6,7]. Highly Active Anti-Retroviral Therapy (HAART) drugs have been associated with decreased Bone Mineral Density

(BMD) especially Tenofovir Disoproxil Fumarate (TDF) and Protease Inhibitor (PI) based regimens. This is probably through the effect of these medications on cellular DNA synthesis and gene expression involved in bone re-modelling[8].

The WHO recommends the use of Dual Energy X-ray Absorptiometry (DXA, previously DEXA) method to determine BMD levels, and has provided guidance on classifying the levels into clinically relevant outcomes depending on the number of Standard Deviations (SDs) below the mean BMD for a healthy, young (25–35 years of age), sex- and ethnicity-matched reference population (T-score).

Other methods used to determine bone mineral density include Quantitative Computer Tomography (QCT) and Quantitative Ultrasound (QUS). Both DXA and QCT involves utilization of specialized equipment, generate ionizing radiation, are expensive and require relative expertise.

Quantitative calcaneal ultrasonography offers several benefits. It is cheaper and more portable than DEXA, there is no exposure to ionizing radiation[10] and is as effective as DEXA at predicting femoral neck, hip, and spine osteoporotic fractures [4,11].

Materials and Methods

This was a hospital based study carried out over a fifteen week period between 4th May and 14th August 2015 at Mbagathi Hospital CCC and VCT Centre. A random generation table was used to select participants from the clinic and VCT Centre of which 105 participants were selected in each arm (total of 315) after satisfying the inclusion criteria for each arm. A questionnaire was administered which captured demographic data, duration of HIV/HAART use and occurrence of traditional risk factors among the respondents. QUS bone mineral density was assessed using a heel ultrasonic gel-coupled QUS system, the Sunlight Mini Omni (Beam Med Ltd, Israel). The participants were asked to remove their shoes and stand with one foot on the ultrasound machine. Three repeated measurements with repositioning was performed on the same foot for all participants. BUA was expressed as a T-score (standard deviations from the mean value in normal young individuals of the same sex) using the manufacturer's age- and sex-specific reference data. A bone densitometry form was filled for each participant showing their bone mineral density.

Results

In this fifteen week study, 105 patients were recruited in the HAART naïve and TDF based HAART regime arms (from Mbagathi CCC) and105 individuals who were HIV negative were recruited from the Mbagathi VCT Centre (Figure 1).

Figure 1: Recruitment process

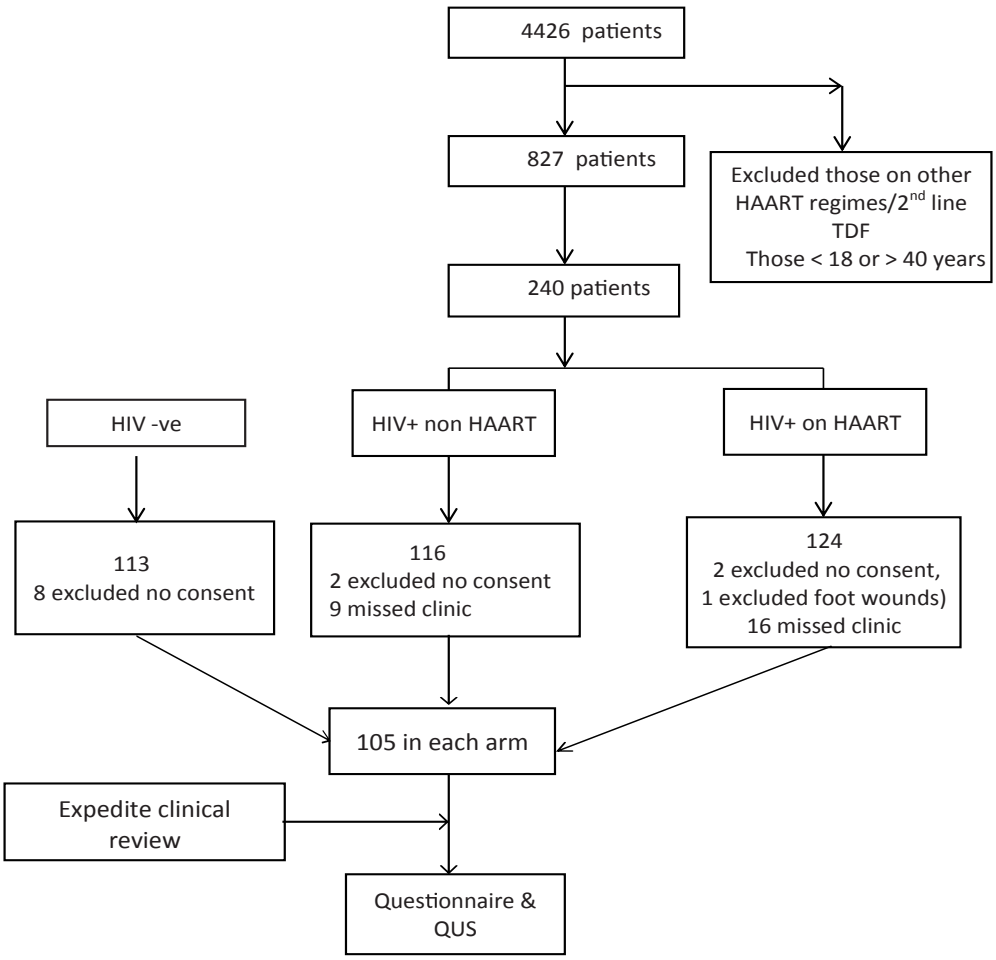
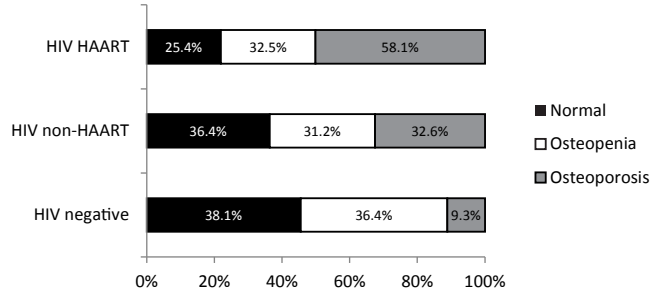


Table 1: Socio-demographic characteristics among the comparative arms

Characteristic	Categories	HIV negative No. (%)	HIV non-HAART No. (%)	HIV on HAART No. (%)	Total (%)
Age (years)	18-22	15(14.1)	13(12.5)	7(6.8)	43.5% (29-28 years)
	23-28	46(44.7)	22(21.1)	15(14.2)	
	29-34	31(29.5)	43(40.6)	31(29.5)	
	35-40	12(11.6)	27(26.8)	52(49.5)	
Gender	Male	48(45.7)	46(43.3)	44(41.4)	137(43.5)
	Female	57(54.3)	59(56.7)	61(58.6)	178(56.5)
Marital status	Married	14(13.2)	32(30.2)	60(56.6)	106(33.7)
	Single	83(52.2)	53(33.3)	23(14.5)	159(50.5)
	Divorced	8(19.5)	18(43.9)	15(36.6)	41(13.0)
	Widowed	0(.0)	2(22.2)	7(77.8)	9(2.9)
Residence	Rural	8(44.4)	1(5.6)	9(50.0)	18(5.7)
	Urban	97(32.7)	104(35.0)	96(32.3)	297(94.3)
Highest education level	None	0(.0)	1(100.0)	0 (.0)	1(0.3)
	Primary	21(20.6)	46(45.1)	35(34.3)	102(32.4)
	Secondary	21(17.1)	50(40.7)	52(42.3)	123(39.0)
	Tertiary	63(60.8)	8(9.0)	18(20.2)	89(28.3)
Occupation	Unemployed	12(25.0)	23(47.9)	13(27.1)	48(15.2)
	Student	60(85.7)	8(11.4)	2(2.9)	70(22.2)
	Self employed	21(17.6)	45(37.8)	53(44.5)	119(37.8)
	Civil servant	3(25.0)	4(33.3)	5(41.7)	12(3.8)
	Other	9(13.6)	25(37.9)	32(48.5)	66(21.0)
Income level per month (Kshs)*	Below 2500	55(51.4)	39(36.4)	13(12.1)	107(34.0)
	2500 - 5000	22(36.1)	25(41.0)	14(23.0)	61(19.4)
	5000 - 10000	16(23.2)	22(31.9)	31(44.9)	69(21.9)
	10000 - 30000	10(14.9)	18(26.9)	39(58.2)	67(21.3)
	>30000	2(18.2)	1(9.1)	8(72.7)	11(3.5)

*1US $ = Kshs 100

Figure 2: Prevalence of BMD abnormalities among comparative arms



The mean T-score of HIV negative respondents was -1.197(±0.168) compared to mean T-scores of -1.311(±0.184) and -1.740(±0.231) in the HIV positive HAART naïve and HIV positive on HAART respondents respectively. There was a significant difference in mean T-score between the comparative arms (ANOVA p-value < 0.001).

Table 2: Socio-demographic characteristics and BMD

Characteristics	Categories	Normal BMD	Ostopenia	Osteoporosis	P- value
Age (years)	18-22	48.1	30.2	21.7	0.032
	23-28	44.5	29.3	26.2	
	29-34	38.4	33.0	28.6	
	35-40	22.0	31.9	46.1	
Gender	Male	39.7%	50.9%	9.5%	0.257
	Female	36.2%	47.7%	16.1%	
Marital status	Married	32.1%	46.2%	21.7%	0.086
	Single	39.6%	52.8%	7.5%	
	Divorced	36.6%	46.3%	17.1%	
	Widowed	66.7%	22.2%	11.1%	
Residence	Rural	33.3%	38.9%	27.8%	0.195
	Urban	37.7%	49.5%	12.8%	
Highest education level	None	100.0%	0.0%	0.0%	0.756
	Primary	36.3%	47.1%	16.7%	
	Secondary	39.8%	48.0%	12.2%	
	Tertiary	34.8%	52.8%	12.4%	
Occupation	Unemployed	41.7%	45.8%	12.5%	0.280
	Student	38.6%	55.7%	5.7%	
	Self employed	37.0%	46.2%	16.8%	
	Civil servant	58.3%	25.0%	16.7%	
	Other	30.3%	53.0%	16.7%	
Income level per month (Kshs)*	Below 2500	40.2%	49.5%	10.3%	0.798
	2500 – 5000	34.4%	47.5%	18.0%	
	5000 – 10000	39.1%	44.9%	15.9%	
	10000 – 30000	37.3%	50.7%	11.9%	
	>30000	18.2%	63.6%	18.2%	

* 1 US $ = Kshs 100

There was significant negative correlation between T-score and age of the respondents (Spearman r = -.121, p-value = 0.032). This implied that older patients were associated with lower levels of BMD (i.e. more negative BMD). There was no significant association between low BMD and marital status (p-value = 0.086), gender (p-value = 0.257), residence (p-value = 0.195), highest education level (p-value = 0.756), occupation (p-value = 0.280) and income level per month (p-value = 0.798).

Table 3: Traditional risk factors distribution among the comparative arms

Risk factor	HIV Negative	HIV Non HAART	HIV on HAART
Oral corticosteroid use	3.8%	1.9%	0%
Current smokers (n=11)	6.7%	1.9%	1.9%
Used to smoke (n=33)	8.6%	7.6%	15.2%
Alcohol intake (n=160)			
Once monthly or less (n=122)	50.4%	45.7%	20.0%
Weekly(n=35)	19.0%	8.6%	5.7%
Daily (n=3)	1.9%	0.9%	0.0%
Sustained bone fracture	16.1%	20.0%	13.3%
Physical activity levels			
Vigorous	22.8%	13.3%	14.2%
Moderate	43.9%	35.3%	45.7%
minimal	33.3%	51.4%	40.0%
BMI(Kg/m²)	26.1	24.8	23.6

Body Mass Index (BMI): There was a significant difference in BMI among the comparative arms (ANOVA p-value < 0.001) with HIV negative patients having significantly the highest BMI on average followed by HIV non-HAART then HIV HAART patients. There was significant positive correlation between T-score and BMI (Pearson R = 0.085, p-value = 0.043).

Table 4: Multivariate analysis

Variable	Significance	Odds Ratio	95% C.I. for Odds Ratio	
			Lower	Upper
Age in years	0.364	1.017	.981	1.053
BMI (Ref≥25)	0.046	1.962	1.607	2.225

Multivariate analysis: Factors that were significant at the bivariate stage (age and BMI) underwent multivariate analysis to identify the predictors of decreased bone mineral density. BMI was the only risk factor identified as significant to predict occurrence of decreased bone mineral density at (p-value of 0.046) (Table 4).

Discussion

Our study populations were adults between 18-40 years old with a female preponderance of 56.5%. This was in keeping with our national HIV demographics[1,3]. Though we did not match age and gender among the comparative arms (resource constraints), our study showed a significant negative correlation between T-score and age of the respondents. This implied that older respondents were associated with lower Bone Mineral Density (BMD) levels. John *et al*[13] attributed this to age related changes in bone homeostasis and increased bone fragility.

Our study showed that the prevalence of osteoporosis among HIV positive respondents on HAART was significantly higher as compared to HIV positive respondents not on HAART and HIV negative respondents. Our study showed 58.1%, 32.6% and 9.3% of those on HAART, HIV positive HAART naïve and HIV negative respondents respectively were osteoporotic. This reflects a six-fold higher prevalence of osteoporosis between HIV infected individuals and the HIV negative controls. In other studies comparing HIV infected to uninfected populations the T-score difference between the two groups (HIV infected and uninfected) varied from 2.5-fold to 10-fold[14-17].

Flöter *et al*[18] in a review of six comparative studies between DEXA and QUS of the calcaneus concluded that the QUS sensitivity (79% to 93%) and specificity (28% to 90%) had wide variations which may lead to over or under diagnosis of bone density abnormalities at the WHO recommended T-score cut off of ≥ 2.5. He also noted that the diagnostic accuracy may be improved by varying the cut off T-score. This could partly explain the high rates of bone mineral density abnormalities in our study.

QUS and DEXA simply measures different bone characteristics (bone quality and bone quantity respectively). QUS can thus determine the strength of bone micro-architecture which may be associated with impaired bone structure with a higher risk of fractures and lower BMD[19]. QUS parameters including Speed of Sound (SOS), Bone Ultrasound Attenuation (BUA) and bone stiffness provide additional, specific and different information which may be useful in the integrative assessment of bone health[20].

It is also important to note that QUS has been extensively researched in large prospective studies and meta-analyses and has demonstrated comparable utility and diagnostic accuracy to DEXA at hip and non-spinal bone sites [21-27].

In our study, the prevalence of osteopenia was 32.5%, 31.2% and 36.4% in those HAART, HIV positive HAART naïve and HIV negative respondents respectively. This was in keeping with a meta-analysis of 37 studies by Brown *et al*[4] which showed significant heterogeneity between the studies for reduced BMD with osteopenia of between 4% - 56% in the HIV negative respondents and 13% - 62% in the HIV positive respondents on HAART. Poor dietary intake of calcium rich foods especially in childhood and adolescence could explain the similar rates of osteopenia across the comparative arms[12].

Several studies[4,28] have shown the association of Tenofovir Disoproxil Fumarate (TDF) with nephrotoxicity and hypophosphatemia due to renal tubular dysfunction leading to impaired Vitamin D metabolism which may determine low BMD in HIV patients.

HIV infection has been associated with decreased BMD mainly through cytokine dysregulation and impaired Vitamin D metabolism[29-32]. Thus the longer duration of living with HIV may be associated with low BMD[33]. We did not find significant association between T-score values and length of living with HIV which could be attributed to the relatively short duration of living with HIV among the respondents, with a mean duration of 4.8 years. Body Mass Index (BMI) was 23.6%, 24.8% and 26.1% among HIV positive on HAART, HIV positive HAART naïve and HIV negative respondents respectively. We did find a significant negative correlation between T-score and BMI. Respondents with low BMI were likely to have lower BMD values.

The difference in Bone Mineral Density (BMD) abnormalities was in part, related to the difference in Body Mass Index (BMI) between those on HAART and HIV negative respondents. Bone mass is known to be positively correlated with BMI, as an indicator of muscular mass, and HIV infected individuals usually have lower body weight compared with uninfected persons[34,35]. A meta-analysis by Bolland *et al*[36] showed that, after adjustment for weight, residual between-group differences in bone mineral density were small (2.2-4.7%) and unlikely to be clinically significant.

Poor dietary intake of milk especially in childhood and adolescence has been associated with low bone mineral density [12,37]. This could partly explain low BMD in our study participants who are from a low socioeconomic catchment area.

Most longitudinal studies involving HAART-naïve individuals showed that bone mineral density declined by 2-6% within 24-48 weeks after initiation of HAART[38-41]. Thereafter, bone mineral density values remained stable or

even increased slightly[42]. We did not find any association between QUS bone mineral density and duration of treatment with HAART. This could be attributed to the fact that majority of the respondents (68%) had received HAART for at least 45 months.

Persons who consume moderate amounts of alcohol have a lower risk of hip fractures compared to heavy drinkers[43]. We did not find significant difference in bone mineral density in the respondents who consumed alcohol. This could be due to the fact that 50.8% of the total respondents in our study took alcohol of whom76.3% consumed alcohol once a month or less and only 0.9% of the study participants who consumed alcohol daily.

Karnis *et al*[44] in a multi-center prospective study concluded that the risk of fractures is greater for smokers and those with a history of smoking compared to non-smokers. We did not find significant difference in BMD between those who smoked, had prior history of smoking and non-smokers. There was also no significant correlation between pack years smoked and BMD. This could be attributed to the fact that only 3.5% of the total respondents smoked, with 2.7 average pack years and a study population of young adults.

We did not find any association between oral corticosteroid use with decreased BMD. This could be attributed to the low number of respondents on oral corticosteroids (5.7%), though duration of steroid use and preventive measures against steroid induced osteoporosis (vitamin D and calcium supplementation use) was not assessed. Further studies are required to determine the relationship of duration of corticosteroid use with BMD in the HIV population. 43.9%, 45.3% and 45.7% of HIV negative, HAART naïve and those on TDF based regime respectively were involved in moderate physical activities. We did not find any difference in BMD values in the intensity levels of physical activity among the comparative arms. This could be attributed to the fact that the respondents were from a low socio-economic background (53.4% earned <kshs 5000 or US$50/month) and could not afford public transport and would therefore walk to work.

We have shown, in an African setting, that HIV infected patients on a TDF based regime have reduced Quantitative Ultrasound bone mineral density in comparison to HAART naïve and HIV negative populations. However, the clinical significance of this result in terms of osteoporosis remains unknown, since we could not use the validated reference method by WHO for bone mineral density assessment.

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Osteoporosis in rheumatic diseases

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Abstract

Background: Inflammatory joint disease such as rheumatoid arthritis, as well as other rheumatic conditions, such as Systemic Lupus Erythematosus (SLE) and ankylosing spondylitis comprise a heterogeneous group of joint disorders that are all associated with extra-articular manifestations, including bone loss and fractures.

Objectives: Evaluation of osteoporosis burden on patients with rheumatic diseases by determining the frequency of osteoporosis among those patients and to study the risk factors of osteoporosis in patients with rheumatic diseases.

Methods: The inclusion criteria for the study were all patients who were diagnosed to have rheumatic diseases that attended to Rheumatology Clinic of Tripoli Medical center, Tripoli, Libya, for follow up in the period from May 2013 to December 2013. Dual Energy X-ray Absorptiometry (DEXA) scan for the lumber spine and the hips was done for all patients. Demographic details such as age, sex and menopausal status were recorded. Clinical characteristics such as drugs used for every patient, steroid maintenance dose and duration of taking steroid were noted. Other clinical data as history of previous fractures and family history of osteoporosis were also determined.

Results: The study included 100 patients who had rheumatic diseases and followed in rheumatology out patients' clinic. Osteoporosis was detected in 37/100 (37%) of patients. Osteopenia occurred in 51/100 (51%) of patients. Normal DEXA scan presented in 12/100 (12%) of the patients. Thirty seven patients who had osteoporosis, 5/37 (13.5%) were male and 32/37 (86.4%) were female. Thirty two female patients, 4/32 (12.5%) were in premenopausal age and 28/32 (87.5%) were in postmenopausal age. Most patients who had osteoporosis, 32/37 (86%) were taking steroid in form of prednisolone tablets. Previous fractures occurred in 4/37 (10.8%) of osteoporotic patients. Family history of osteoporosis was found in 4/37 (10.8%).

Conclusion: Presence of osteoporosis in 37% and osteopenia in 51% of our patients indicate a large burden of osteoporosis on patients with rheumatic diseases. Multiple risk factors of osteoporosis present in our patients, family history of osteoporosis in the first degree relatives in 10.8%, previous history of factures in 10.8% and long term use of corticosteroid treatment in 86%.

Keywords: Osteoporosis, Rheumatic diseases

Introduction

Inflammatory joint disease such as rheumatoid arthritis, as well as other rheumatic conditions, such as Systemic Lupus Erythematosus (SLE) and ankylosing spondylitis comprise a heterogeneous group of joint disorders that are all associated with extra-articular manifestations, including bone loss and fractures[1].

The concept of osteoimmunology is based on growing insight into the links between the immune system and the bone[1]. The pathogenesis of osteoporosis in rheumatic diseases is multifactorial[1].

Several cross-sectional studies reported that disability and reduced motility that are due to functional impairment are among the most important detrimental effect of uncontrolled disease activity on bone density. In this perspective, the suppression of inflammation probably remains the main concern when considering the treatment options[2].

A better appreciation of the impact of osteoporosis in rheumatic disease by rheumatologists represent a clinical challenge, however, a greater understanding of this frequent complication will improve the quality of health care and the lives of patients who have rheumatic diseases.

Materials and Methods

The inclusion criteria for the study were all patients who were diagnosed to have rheumatic diseases that attended to Rheumatology Clinic of Tripoli Medical Center, Tripoli, Libya, for follow up in the

period from May 2013 to December 2013 and consented to participate in the study. The study was done after receiving consent from Tripoli Medical Center ethical and research committee.

Dual Energy X-ray Absorptiometry (DEXA) scan for the lumber spine and the hips was done for all patients. Osteopenia, defined as a T-score in the lumber spine and /or hips between -1 and -2.5. Osteoporosis was defined as a T-score less than -2.5. Demographic details such as age, sex and menopausal status were recorded. Clinical characteristics such as drugs used for every patient, steroid maintenance dose and duration of taking steroids were noted. Other clinical data such as history of previous fractures and family history of osteoporosis were also determined.

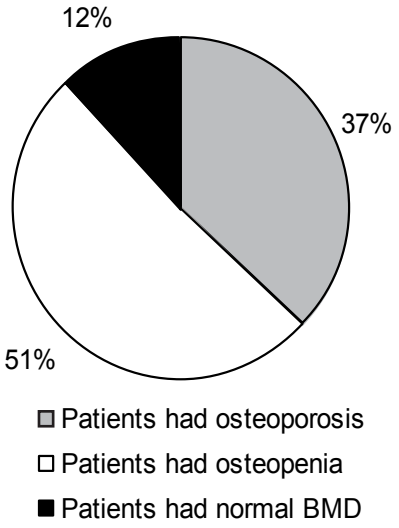
Data analysis: Data was analyzed using SPSS computer soft ware package. Continuous variables were categorized in ranges and summarized into mean, median and standard deviations.

Objectives: Evaluation of osteoporosis burden on patients with rheumatic diseases by determining the frequency of osteoporosis among those patients and to study the risk factors of osteoporosis in patients with rheumatic diseases.

Results

The study included 100 patients who had rheumatic diseases and followed in rheumatology out patients' clinic. Osteoporosis detected in 37/100 (37%) of patients. Their mean age was 54.97 ± SD 11.75) years and the median was 55 years (range 36 - 76 years). Osteopenia occurred in 51/100 (51%) of patients. Normal DEXA scan was presented in 12/100 (12%) of patients (Figure 1).

Figure 1: Distribution of the results of DEXA scan in 100 rheumatic diseased patients



Thirty seven patients who had osteoporosis, 5/37 (13.5%) were male (all were smokers and not alcoholics) and 32/37 (86.4%) were female (all were neither smokers nor alcoholics). Thirty two female patients, 4/32 (12.5%) were in premenopausal age and 28/32 (87.5%) were in postmenopausal age (Table 1).

Table 1: Demographic characteristics of 37 osteoporotic patients

Age (years)	
Mean (SD)	54.97 (± SD 11.75)
Median (Range)	55 (36 - 76)
Sex (No.,%)	
Female	32 (86.4%)
Male	5 (13.5%)
Menopause status (No.,%)	
Premenopause	4 (12.5%)
postmenopause	28 (87.5%)

In 37 osteoporotic patients, 9/37 (24%) had systemic lupus erythematosus (mean age was 42 years, 72% were female and 29% were male), 24/37 (64%) had rheumatoid arthritis (mean age was 59 years, 96% were female and 4% were male) and 2/37 (5%) had Behcet's disease (mean age was 50 years and 100% were male). Other diseases were systemic sclerosis, polymyositis, primary Sjogren's syndrome, overlap syndrome, gouty arthritis and psoriatic arthritis, osteoporosis occurred in 1/37 (2.7%) in each disease.

Drug history of those patients was as follows: prednisolone was taken by 81% of patients, 59% of patients were taking methotrexate, 19% were taking hydroxychloroquine, 13.5% were on leflunomide, 5% were on salazopyrine, 2.7% were on azathioprine and 2.7% were on cyclophosphamide. Regarding anti-osteoporotic therapy, 46% were on bisphosphonates and 2.7% were on denosumab. Forty six percent of patients were taking vitamin D and 43% were taking calcium tablets. All 37 osteoporotic patients had Bone Mineral Density (BMD) ≤ 2.5 in the lumber spine and 7/37 (19%) had BMD of ≤ 2.5 in both the lumber spine and the hips. Previous fractures occurred in 4/37 (10.8%) of osteoporotic patients, 2 patients had radius fracture and 2 patients had leg fracture. Family history of osteoporosis was found in 4/37 (10.8%).

Discussion

In our study, half of our patients with rheumatic disease had osteopenia, more than one third had osteoporosis and only 12% had normal bone densitometry, this reflects the great burden of osteoporosis on our patients. In a subgroup analysis of patients with rheumatoid arthritis, bone loss in both the spine and the hips was much larger in those patients with high C-Reactive Protein (CRP) levels (>20mg/dl) (eg, in the spine,-2.1% vs 0.2% respectively). The same was found in the lumber spine for patients with low functional capacity (Health Assessment Questionnaire [HAQ] score >1) compared with patients with a better HAQ score <1) (-1.9% vs -0.2%, respectively).

Unmodifiable risk factors for osteoporosis include a personal history of a fracture after the age of 40 years, first degree relative with a history of facture, white or Asian race, weight less than 127 pound, height more than 5 feet and 7 inches and advanced age. Modifiable risk

factors included inadequate intake of dietary calcium and vitamin D, low testosterone levels in men, pre-menopausal estrogen deficiency, cigarette smoking, excess alcohol intake, impaired vision, neurologic disorders, lack of sunlight and physical inactivity.

Secondary causes of osteoporosis include gonadal deficiencies, medical conditions altering bone turn over (rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis) and medications interfering with bone metabolism (corticosteroids, methotrexate, cyclophosphamide)[4]. In our osteoporotic patients, 10.8% had previous history of factures, 10.8% had history of osteoporosis in their first degree relatives and 86% were on corticosteroid treatment.

General lifestyle measures are important for all patients with rheumatic diseases: an adequate calcium intake, prevention of falls, adequate vitamin D levels and prevention of immobilization, if possible. Special attention must be paid to sufficient serum 25(OH)D levels in SLE patients because of photosensitivity. In addition, the prescription of adequate immunosuppressive medication to reduce inflammation-induced bone loss is important, which has been documented in RA. Unfortunately, intervention studies demonstrating the effectiveness of one of the available anti-osteoporotic drugs (eg. bisphosphonates) for fracture reduction in patients with RA, SLE, or AS have not been performed yet[5].

Bisphosphonates are recommended for the prevention and treatment of osteoporosis in corticosteroid treated patients. Another point is the use of bisphosphonates during long-term use of corticosteroids. Although bisphosphonates are effective in the initial phase of treatment, their use in long-term can be criticized[6]. Fundamental studies have elucidated that the upregulated RANKL, with subsequent activated osteoclastogenesis, is an important determinant of bone loss in RA. Denosumab, a monoclonal antibody against RANKL, is an attractive new therapeutic agent for osteoporotic patients with RA. Not only has an increase in BMD of the spine and the hips been demonstrated in RA patients, but also a strong reduction in joint erosions[1]. Clinical studies have demonstrated that adequate immunosuppressive therapy (eg. According to the treat to target principle) prevent both local and generalized bone loss.

Conclusion

(i) Presence of osteoporosis in 37% and osteopenia in 51% of our patients indicate a large burden of osteoporosis on patients with rheumatic diseases.
(ii) Multiple risk factors of osteoporosis present in our patients, family history of osteoporosis in the first degree relatives in 10.8%, previous history of factures in 10.8% and long term use of corticosteroid treatment in 86%.
(iii) Control of disease activity and use of preventive measures of osteoporosis are important factors to decrease osteoporosis risk in rheumatic patients.

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Research article

Haematological parameters in systemic lupus erythematosus patients at Kenyatta National Hospital, Nairobi

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Abstract

Background: Haematological abnormalities are the most common manifestations of Systemic Lupus Erythematosus (SLE). Anaemia of Chronic Disease (ACD) has been associated with significantly higher disease activity. Thrombocytopenia early in the course of disease is indicative of more severe active disease and if severe it is an independent predictor of damage accrual and mortality. Leucopenia usually reflects disease activity.

Objectives: To determine the prevalence of haematological abnormalities, among SLE patients on follow up at Rheumatology and Renal Outpatient clinics at Kenyatta National Hospital. Specifically, the study aimed to describe the prevalence of anaemia, leucopenia, and thrombocytopenia and identify patient factors associated with these abnormalities.

Design: Cross-sectional hospital based descriptive study.

Setting: Rheumatology out-patient clinic and Renal out-patient clinic at KNH.

Subjects: Sixty five patients who fulfilled the 1997 American College of Rheumatology Classification Criteria for SLE.

Results: Sixty five eligible SLE patients were recruited into the study. The mean (SD) age was 36.5 (± 12) years. There were 3 (5%) males and 62 (95%) females. Forty nine (75%) patients had at least one abnormality. The abnormalities involved all the three cell lines. The prevalence of abnormalities were; anaemia 43%, leucopenia 26% and thrombocytopenia 20%.

Conclusion: Haematological abnormalities were the second most common manifestation of the disease after arthritis and arthralgia among SLE patients on follow up at Kenyatta National Hospital Rheumatology and Renal clinic. Though majority of these abnormalities were mild to moderate and clinically asymptomatic, the proportions of anaemia, leucopenia and thrombocytopenia were substantially high.

Key words: Haematological parameters, Systemic Lupus Erythematosus, Kenyatta National Hospital

Introduction

Systemic Lupus Erythematosus (SLE) is an autoimmune disorder that results in multi-systemic inflammatory damage. It's often severe and can affect virtually all organs including the haematologic system.

Haematological abnormalities have been noted to be among the commonest in SLE patients in several studies[1,2]. This is attributed to blood and blood vessels together containing more diverse number of antigens than any other organ in the body and in SLE auto antibodies are known to develop against any antigen or tissue. Haemolytic anaemia, leucopenia, lymphopenia, and thrombocytopenia are part of the diagnostic criteria for SLE according to American College of Rheumatology criteria (ACR) 1997[3] and the more recently validated Systemic Lupus International Collaborating Clinics Classification Criteria (SLICC) 2012 for Systemic Lupus Erythematosus[4].

SLE patients with Anaemia of Chronic Disease (ACD) have been shown to have significantly higher disease activity[5]. Thrombocytopenia early in the course of SLE is indicative of more severe active disease, if severe it is an independent predictor of damage accrual and mortality[6,7]. Leucopenia is also common in SLE and usually reflects disease activity[7,8].

Different studies report different prevalence rates. Agrawal *et al*[9] in Central India in 2012 reported haematologic manifestation in SLE in 72.4% of patients while Houman *et al*[10] in Tunisia reported a prevalence rate of 81%.

Materials and Methods

A cross sectional descriptive hospital based study conducted between March 2015 to June 2015 at Rheumatology and Renal outpatient clinics of Kenyatta National Hospital (KNH). The study was commenced after obtaining all the necessary ethical approvals from the KNH research and ethics committee and from the Department of Clinical Medicine and Therapeutics, University of Nairobi. All

patients aged above 18 years seen at KNH Rheumatology and Renal clinics fulfilling the 1997 ACR classification criteria for diagnosis for SLE were eligible. All patients gave an informed written consent. Consecutive sampling method was applied.

Targeted clinical history and physical examination was done. Approximately 4ml of venous blood was drawn aseptically, following standard guidelines from each patient for measurement of a complete blood count, reticulocyte count, erythrocyte sedimentation rate and peripheral blood film examination. The tests were undertaken at the KNH Department of Human Pathology, Unit of Haematology and Blood Transfusion using a CELL-DYN 3700 automated blood counter. ESR interpretation was undertaken at the same laboratory by the Wintrobe method and a PBF was reported after staining with maygrunwald / giemsa stain by direct visualization on a microscope at various powers of magnification by a haematologist.

Statistical analysis was done using SPSS version 21. Analysis included descriptive statistics such as means, medians and standard deviation for continuous variables and frequency distributions for categorical variables, with their corresponding 95% Confidence Intervals (CI). Comparisons for continuous data was made using the t-test, and of categorical data using the chi-square test. Prevalence of study variables, (e.g. anaemia, leukopenia and thrombocytopenia) was calculated as the proportion of subjects having the variable divided by the total number of subjects. Precision was indicated by 95% Confidence Interval (CI) limits. A p value ≤ 0.05 was considered significant. The final results were presented in tables, charts and graphs.

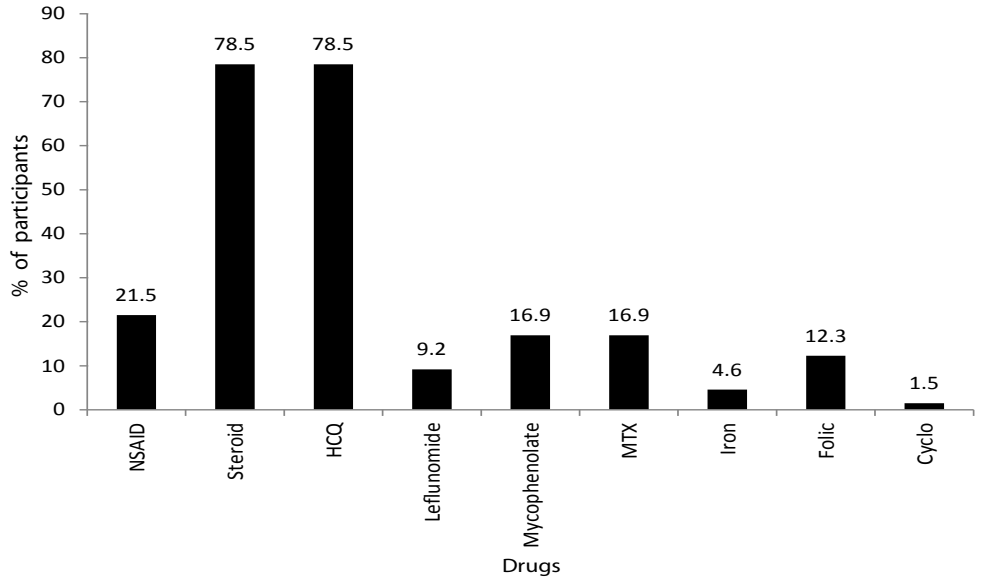
Results

In a period of 4 months (March 2015 to June 2015) 71 patients with SLE were identified, of these 66 met the ACR criteria for SLE and were recruited to the study. Three patients had SLE and Rheumatoid Arthritis (RA) while two had SLE with Mixed Connective Tissue Disease (MCTD) and were excluded. One patient was eligible but refused to give consent to have blood tests done. Final analysis included 65 patients.

Table 1: Baseline characteristics of the study population

Characteristic	Frequency(%)
Sex	
Male	3 (5%)
Female	62 (95%)
Age (years)	
Mean (SD)	36. 5 (± 12)
Range	18-62
Median	35
Age distribution (years)	
>20	7 (11%)
21-40	36 (55%)
>41	22 (34%)
Age at diagnosis	
Mean (SD)	33 (±12)
Duration of disease in months	
Median (IQR)	36 (12-60)
Level of education	
Primary	14 (21.5%)
Secondary	36 (55.4%)
Tertiary	15 (23.1%)
Occupation	
Employed	15(23.0%)
Self employed	25(38.5%)
None	25(38.5%)
Residence	
Urban	28(43.1%)
Rural	37(56.9%)

Figure 1: Medications taken by study participants



NSAID = Non Steroidal Anti-inflammatory drugs), HCQ = Hydroxychoroquine), MTX = Methotrexate, Cyclo = Cyclophosphomide

Table 2: Haematological parameters of study participants (n=65)

Parameter	Median (Range)	Mean±SD	Ref Range (Male)	Ref Range (female)
RBC (x10^{12}/L)	4.5 (1.9-5.9)	4.3 (0.8)	4-6	3.5-6.5
Haemoglobin (g/dl)	12.4 (5.4-17.9)	12 (2.6)	13.5-18	12-15
WBC (x 10^9 /L)	5 (1.1-17.1)	6.2 (3.3)	4-11	4-11
Neutrophil (x 10^9/L)	2.8 (0.1-14.8)	3.7 (2.7)	2.0-7.5	2.0-7.5
Lymphocytes (x 10^9/L)	1.6 (0.3-6.4)	1.8 (1.1)	1.5-4.0	1.5-4.0
Platelets (x 10^9/L)	266 (28-521)	263.8 (107)	150-400	150-400
ESR (mmhr)	30 (1-122)	38.2 (28)	0-9	0-20

Figure 2: Prevalence of haematological abnormalities in SLE

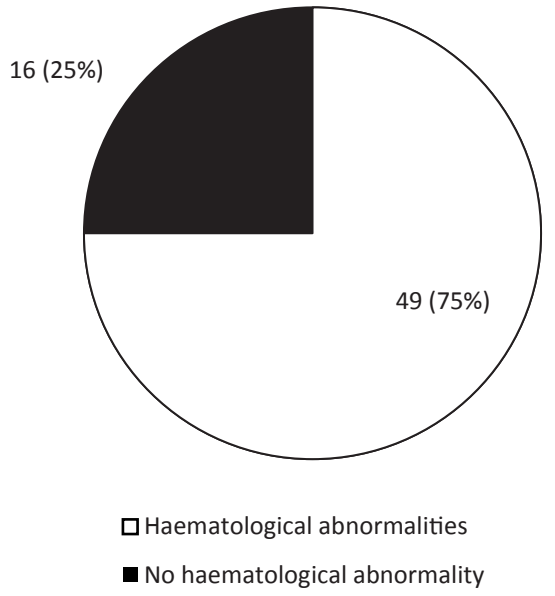


Table 3: Prevalence of various haematological abnormalities amongst study participants (n=65)

Abnormality	Frequency	(%)	95% CI
Anaemia	28	43.1	30.7-55.4
Leucopenia	17	26.2	15.2-37.1
Neutropenia	18	27.7	17.3-40.2
Lymphocytopenia	29	44.6	32.2-57.5
Leucocytosis	6	9.2	2-16.5
Neutrophilia	6	9.2	2-16.5
Lymphocytosis	3	4.6	112.9
Thrombocytopenia	13	20	10-30
Thrombocytosis	8	12.3	4.1-20.5

Figure 3: Type of anaemia in study participants

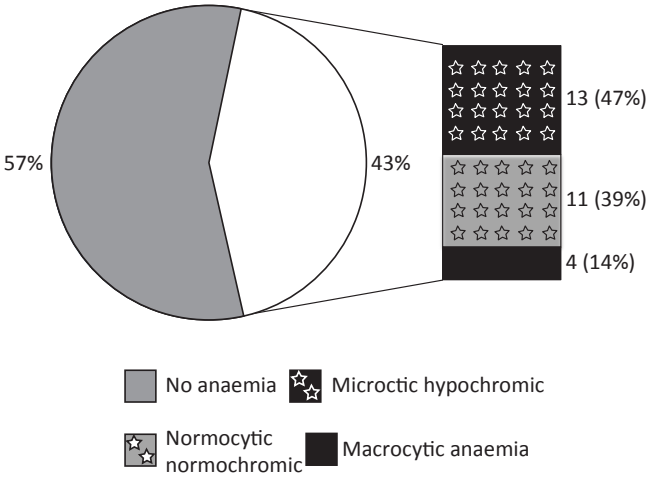
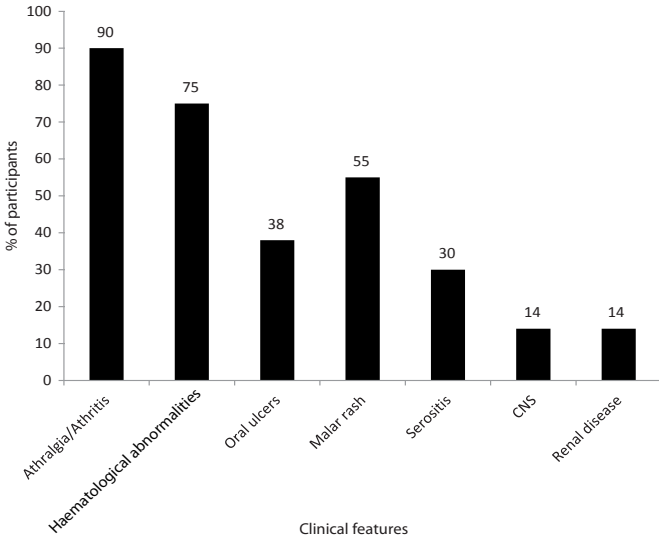


Figure 4: Distribution of clinical features of SLE in the study population



CNS = Central Nervous System

Discussion

Haematological abnormalities: In this study haematological abnormalities were the second most common manifestations (75%) of SLE after athralgia and arthritis. Anaemia was the commonest abnormality present in 43% of patients followed by leucopenia (26%) and thrombocytopenia (20%). Severe haematological involvement has been associated with significant CNS and renal disease[11] and this raises a concern of possible severe disease in our SLE population.

The prevalence of haematological abnormalities in this study was comparable to what has been found in other studies conducted in other parts of the world. In Nigeria, Houman *et al*[10] found a prevalence rate of 81%. Several studies done in India among them Agrawal *et al*[9] found a prevalence 72.4% and Sasidharan *et al*[12] found prevalence of 82%. Western literature also indicates haematological abnormalities are a common presentation of SLE[13]. These findings support our observation and emphasizes that haematological abnormalities are a common manifestation of SLE patients.

Anaemia: Anaemia was present in 43.1% of the patients. Although the mean haemoglobin was 12g/dl, and the median was 12.4g/dl, the haemoglobin range was 5.4 - 17.9g/d. The aetiology of anaemia in SLE is usually heterogeneous and may result from immune and non immune mechanisms. Some of the possible causes of anaemia in our population are Iron Deficiency Anaemia (IDA), Anaemia of Chronic Disease (ACD), Autoimmune Haemolytic Anaemia (AIHA), and drug induced myelotoxicity. Other rare causes eg aplastic anaemia and myelofibrosis may also have contributed to anaemia in our SLE population. ACD in our population may have been due to chronic inflammation and renal disease while IDA may have been due to menorrhagia as most of our participants were young females in the reproductive age group, gastrointestinal bleeding due to the frequent use of NSAIDS and steroids, nutritional and possibly due to hookworm infestations.

The prevalence of anaemia in this study is lower than that found by Sasidharan *et al* [12] in India. They found an anaemia prevalence of 62%. This could be attributed to co-existing high prevalence of anaemia in India (approximately 50%) in the rural areas as compared to Kenya's prevalence of 38%, (WHO global data base on anaemia burden[14]). The reason given for the high anaemia burden among Indians are nutritional related being predominantly vegetarian society with limited nutritional iron sources and chronic blood loss from hookworm infestations in rural areas. This study population was predominantly urban. Additionally the study focussed on a highly preselected population which was being followed up in a tertiary setting with improved care and ability to access quality health care.

Anaemia in SLE is largely multifactorial but morphologically most of the study population had microcytic hypochromic anaemia. Microcytic anaemia is usually due to either IDA or less commonly ACD. These findings differ with other studies in other centers where normocytic normochronic anaemia has been found to be most common[12]. The high prevalence of microcytic anaemia can be explained by increased number of patients on steroids, NSAIDS and antimalarials. Other possible cause could be due to our study population consisting of predominantly young females in the reproductive age group.

Despite the high prevalence of moderate anaemia (20%) in our study population only a small proportion of patients were on treatment with hematinics, such as iron (4.3%) and folic acid (12.2%) indicating that anaemia in this group was largely untreated. Folic acid was co-prescribed with methotrexate. None of the patients was on erythropoesis stimulating agents.

White cell abnormalities: The mean white cell count in the study population was 6.2 x 10^9/L a median of 5 x 10^9/L and a range 1.1-17.7 x 10^9/l. However in Africans a lower limit of normal WBC of 2.6 X 10^9/ L has been described[15].

Leucopenia: Leucopenia in this study was defined using the haematology laboratory reference range as WBC count < 4 x 10^9/L. The prevalence of leucopenia was 26.2%, mainly due to lymphopenia and neutropenia. Immune destruction of antibody coated WBC, active disease and steroid therapy may have contributed to leucopenia in our population. Several studies have shown leucopenia is associated with active disease and steroid therapy[16]. Neutropenia in our population was largely multifactorial; it may have been due to immune mediated mechanism by anti-neutrophil antibodies, medications (e.g.azathioprine), bone marrow dysfunction, or hypersplenism. Several studies have demonstrated these possible mechanisms[16].

Leucopenia in this study was more pronounced than in the Indian study by Sasidharan *et al*[12]. Sasidharan's study found a leucopenia prevalence of 15.7% while Agrawal *et al*[9] found a prevalence of 18.4%. This difference in leucopenia could be attributable to the racial differences between the two populations. Black Africans have been found to have a slightly lower WBC count than other races[15]. Several studies have shown leucopenia is associated with active disease and steroid therapy[16]. Leucopenia in the study participants could be due to both active disease and steroid therapy.

Leucocytosis: Leucocytosis was present in 9.2% of study population, majorly driven by neutrophilia. We attributed this to the high proportion of patients who were on steroids. Other possible explanation is the patients may have had active infection.

Platelet abnormalities: The mean platelet cell count in the study population was 263.8 x 10^9/L, a median of 266 x 10^9/L and a range 28-521 x 10^9/ L.

Thrombocytopenia: Thrombocytopenia was defined using the haematology laboratory reference range as platelet count < 150 x 10^9/L.

Several mechanism may have contributed to thrombocytopenia in our population among them immune destruction, drugs, infections and possibly bone marrow suppression. Thrombocytopenia in our study population was most of the time mild and benign and not associated with any overt bleeding. These patients did not require any specific treatment. Nevertheless since thrombocytopenia is an independent risk factor for mortality[16], the sub-group of patients with thrombocytopenia will require more aggressive management and more frequent follow up.

In their Indian study, Sasidharan *et al*[12] found a thrombocytopenia prevalence of 39.8% in SLE patients. The prevalence of thrombocytopenia in this study was 20% which was significantly lower. This difference could be partly due to the fact that their study looked at thrombocytopenia as an initial presentation of SLE while in this study platelets counts were measured among participating patients at different times in the course of their illness. In addition majority of our patients were already on treatment and had achieved some control of the disease. Agrawal *et al*[9] in their study found a lower prevalence of thrombocytopenia of 14.9%. However it is notable that in Agrawal's study, thrombocytopenia was defined as a platelet count below 100 x10^9/ L as opposed to this study where we defined thrombocytopenia as a platelet count below 150 x 10^9/ L.

Thrombocytosis: There were 8 cases (12.3%) of thrombocytosis of which 3 cases had confirmed APLAS. The other 5 cases had not been investigated for APLAS. A plausible explanation for this is a possible reactive thrombocytosis in our study population due to the high prevalence of microcytic hypochromic anaemia.

Our prevalence of 12.3% was significantly higher than that reported in other studies. Castellino *et al*[17] found a prevalence of 3.7% in Caucasians with SLE. These differences may be attributed to racial differences.

Erythrocyte Sedimentation Rate: The mean ESR 38.2mm/ hr with a median of 30mm/hr and range of 1-122mm/hr. Majority of the patients (66%) had an elevated ESR. This may be explained by the high prevalence of anaemia at 43.1%. Other possible causes are the patients may have had active disease as several studies have shown that elevated levels of ESR may be associated with disease activity and accumulated damage[18].

Conclusion

Haematological abnormalities were the second most common manifestation of the disease after arthritis and arthralgia among SLE patients on follow up at Kenyatta National Hospital Rheumatology and Renal clinic. Though majority of these abnormalities were mild to moderate and clinically asymptomatic, the proportions of anaemia, leucopenia and thrombocytopenia were substantially high.

Study limitations

Our analysis did not scrutinize the causes of haematological abnormalities and correlate our findings with disease activity due to financial constraints.

Recommendations

A study to further scrutinize the causes of these haematological abnormalities needs to be done. A bigger multicenter study to correlate these haematological abnormalities with disease activity in patients with SLE, which may be useful as surrogate markers of disease activity in resource constrained settings. Long term follow up of subgroup of patients who had thrombocytopenia to determine outcome.

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Research article

Itineraries of the rheumatic patients towards the rheumatologist in DR Congo

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Abstract

Objectives: To describe the itineraries of the rheumatic patients towards the rheumatologist.
Methods: A descriptive cross-sectional study was performed in patients attending the rheumatology unit of the University Hospital of Kinshasa from 1st October 2012 to 31st March 2013. Data collected were general demographic parameters, educational level, prior treatment and the delay between the onset of symptoms and the first consultation.
Results: Eighty six patients were included with 53 women (61.6%) and 33 men. Mean age was 52.4 ± 8.3 years and the age at onset symptom was 47.3 ± 7.2 years. Disease duration before rheumatologist consultation was 4.7 ± 4.3 years. The lower age was equal to 55 years, low level of education and female gender were the determinants of the long delay in the consultation of the rheumatologist. Prior treatment consisted primarily of NSAIDs and paracetamol.
Conclusion: Rheumatic patients followed at the UHK generally consult after a relatively long period, therefore delaying the diagnosis and the treatment.

Keywords: Rheumatologist, Itineraries

Introduction

Rheumatic diseases are a common problem in daily medical practice in Africa. They affect all age groups, undertake the functional prognosis of patients and have a significant socio-economic impact[1-3]. Therefore, the early support of these diseases is of great importance, particularly in the inflammatory rheumatism for which the early diagnosis is key to a successful outcome and improve the prognosis and the impact of the quality of life.

Data on the itineraries of rheumatic patients are scarce in Democratic Republic of Congo. The few available studies reported a long delay in diagnosis and treatment of rheumatic patients[2-4]. This delay justified relatively late adequate management, thus with a poor quality of life of these patients and a worse response to treatment[5-7]. The objective of this study was to describe the itineraries of the rheumatic patients attended by a rheumatologist between the onset of the disease and the first consultation in the Rheumatology unit.

Materials and Methods

This was a cross-sectional study at the UHK from 1st October 2012 to 31st January 2013. Patients seen for the first time in the Rheumatology unit were consecutively included. Informed consent was obtained. Patients with inflammatory disease were included in the study.

Data were collected regarding general demographics, delay between the onset of symptoms and the first visit with a rheumatologist, reason for consultation, use of alternative medicine approaches, preceding therapeutic modalities, and the educational level.

The data were recorded using Excel 2010 software and analysed with statistical packages SPSS 17.0. Continuous variable had normal distributions and are presented as means and standard deviations. The other continuous variables had non-normal distributions and are presented as medians. Student's test was used to compare means and the Chi-squared test for comparison of proportions. Simple linear regression analysis was used to determine the correlation between quantitative variables. P-values < 0.05 were considered significant.

Results

During this period, eighty six patients were included in this study. Table 1 shows the general features of the population.

Table 1: Characteristics of the studied population

Characteristic	
Age (mean±SD, year)	52.4±8.3
Age at onset symptom (mean±SD, year)	47.3±7.2
Sex	
Male (n,%)	33 (38.4)
Female (n,%)	53 (61.6)
Disease duration (median, year)	3.2
Disease duration (mean±SD,year)	4.7±4.3
Rheumatism (M/F, mean±SD)	
RA	4/20 (42.0±10.8)
SpA	20/17 (43.2±12.4)
SLE	0/3(28.1±3.4)
SSc	0/1
Dermatomyositis	1/0
JIA	1/1 (13.5±0.4)
Unclassified arthritis	7/11 (36.2±7.6)

RA = Rheumatoid Arthritis, SpA = Sponyloarthritis, SLE = Systemic Lupus Erythematosus, SSc = Systemic Sclerosis, JIA = Juvenile Idiopathic Arthritis

Patients were mostly female (61.6%) with a mean age of 52.4 years. All patients had prior consultations with other caregivers, 73% had a prior consultation with a general practitioner. A high variability was noted between the onset of first symptom and first visit to a rheumatologist, ranging from less than one month to over 4 years.

Table 2: Determinants of the long delay in the consultation

Variables	P-value	OR (IC 95%)
Age (years)		
> 55		
≤ 55	0.013	1.19 (1.02-2.63)
Education		
Secondary and university study	0.002	2.33 (1.34-4.70)
Primary and illiterate		
Gender		
Male	0.012	1.85 (1.15-3.25)
Female		

Pain was the most prominent symptom (92%); swollen joints (30%), articular deformation (13%), extra articular features (11%) were often reported. The majority of patients attempted at least a secondary educational level (80%); only 5% were illiterate. The majority of patients did not have a diagnosis at first consultation with a rheumatologist. Prior treatment consisted primarily of NSAIDs and paracetamol. Minority of patients (15%) had primarily resorted to physiotherapy. Almost half of the patients (47%) had sought help of alternative medicine, especially in the traditional medicine. No case of use of oral corticosteroids or DMARDS was initially reported.

In the univariate analysis, Table 2 shows that female gender, age older than 55 years old and low level of education were the determinants of the long delay in consulting a rheumatologist. Only 15% of the patients were referred to a rheumatologist with a referral letter. The relevance of reference letter came from the general practitioner and other specialists as the ophthalmologists and the dermatologists. Most of the patients had visited a rheumatologist with no satisfactory information from prior treatment.

Discussion

The present study was carried out to describe the itineraries followed by rheumatic patients before consultation to a rheumatologist. Our interest was focused on the course of patients with inflammatory rheumatism for which a long delay to diagnosis would have a real impact on both the functional prognosis that is vital. Mean age of patients was 52.4 years with an average of over 4 years between the onset of symptoms and consultation with a rheumatologist. This long delay before consultation observed in this study was reported in the literature particularly in sub Saharan Africa. Several explanations can be discussed. Firstly, we have noted a problem in the care system organization and the low level of awareness of population on rheumatic diseases. On the other hand, the poverty that characterizes the population does not allow a lot of people accessibility to health care, as well as the lack of a health insurance system. This is among others justified by excessive self-medication, often on the advice of entourage.

Thus, self-medication may be understood by lack of pharmaceutical legislation prohibiting the delivery of drugs without medical prescription. The general practitioner and traditional practitioner were often consulted in case of failure of the auto-medication.

One third of patients were directly referred to a physiotherapist, revealing weaknesses in a system where patients go directly to therapy without a clear diagnosis. Patients with less education would misjudge or ignore altogether the risks of self-medication abuse. They are also easier to turn to traditional medicine which is supposed to cure all diseases, even those that modern medicine considers incurable.

Additionally, a few number of patients (15%) had a referral letter from general practitioners. The role of the female in delayed consultation and the patient itinerary does not appear to have any unique explanation; especially all previous studies conducted in the same area reported a female predominance among rheumatic patients[8,10,12]. We think that one possible reason could be the low income of the woman often depending on that of his husband. Also, the threshold of pain sensitivity appears lower compared to men. A study on a larger sample would clarify this issue.

A relatively long extension of time between the onset of the symptoms and consulting a rheumatologist is reported in several African studies[6-9].

Causative factors were particularly low levels of education, low socioeconomic status and lack of organization of health care systems. In a study of 527 patients with rheumatoid arthritis for example, Hernández-García *et al*[11] had found that the delay in diagnosis varied significantly with marital status, family support, level of education, age at onset of the symptoms, the articular swelling and functional capacity of patients. Feldman *et al*[15] arrived at the same conclusion. Palm *et al*[13] described an association between the delay before the consultation and gender of patients with rheumatoid arthritis.

Conversely, Kumar *et al*[5] in a similar study did not find an association between, firstly, the late consultation and, secondly, age and gender. It is the same for the study of Ibn Yacoub *et al*[14] about 100 patients with ankylosing spondylitis.

Conclusion

The management of rheumatic patients encounters significant delays in our environment. Progress must be done to improve the organization of our system of care in order to minimize the long itinerary taken by the patient to the rheumatologist. The organization of medical screening campaigns of rheumatic diseases in the population to access care in large hospitals could be an asset to reduce this long itinerary.

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Research article

Clinical patterns of juvenile idiopathic arthritis: A single tertiary center experience in Kenya

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Abstract

Background: Juvenile Idiopathic Arthritis (JIA) is a heterogeneous group of disorders with different disease manifestations among various populations. There are few reports of JIA among indigenous Africans in sub-Saharan Africa. We present herein the clinical patterns of JIA encountered at a rheumatology clinic, Nairobi, Kenya.

Method: Medical records of patients with a diagnosis of chronic arthritis with onset at the age of 16 years or less presenting to the Nairobi Arthritis Clinic were reviewed between January 2009 and January 2016. They were retrospectively reviewed and reclassified as Juvenile Idiopathic Arthritis (JIA) based on the International League of Associations for Rheumatology (ILA R) JIA diagnostic criteria.

Results: A total of 68 patients were recruited, the females gender was predominant in all categories of JIA apart from Enthesitis related arthritis. The overall female to male ratio was 2.4:1. The range of age at onset of symptoms was between 2 years and 15 years and the mean age at JIA onset was 8.45 ± 4.37 years. The mean age of presentation at the clinic was 10.22± 3.79 years. Polyarticular rheumatoid factor negative arthritis was most common at 38.2%, followed by oligoarticular 23.5%, polyarticular rheumatoid factor positive 17.6%, systemic JIA at 14.7% and enthesitis associated arthritis at 5.9%. Large joints were affected in 85.2%, small joints 44% and fever was present in 73.5% of patients. One patient had the typical rash of systemic onset JIA (Still's) and another had uveitis. The ESR was raised in all categories of JIA with a mean of 44.35mm/hr while the haemoglobin was reduced with a mean of 10.82mg/dl. Positive Rheumatoid Factor (RF) was found only in RF positive polyarticular JIA. NSAIDs were used in all the patients. NSAIDS were combined with corticosteroids in 38/68 (55.9%) patients while NSAIDs, corticosteroids and methotrexate were used in 16/68 (23.5%) patients and biologics were received by 6/68 (8.8%) patients at different and varying length of time.

Conclusion: This is the first study of JIA undertaken in Kenya. Our patients had a delayed presentation, were predominantly female and sero negative polyarticular arthritis. Challenges experienced in this setting include late presentation to rheumatologists and inadequate resources (personnel, finances, equipment and drugs).

Key words: Juvenile idiopathic arthritis, ILAR, Kenya, Clinical patterns, Treatment

Introduction

Juvenile Idiopathic Arthritis (JIA) is a poorly described disease in Kenyan children. JIA is defined by International League of Associations for Rheumatology (ILAR) as arthritis that begins before the 16th birthday and persists for at least 6 weeks, other conditions being excluded[1]. Literature on the prevalence and incidence of JIA suggest that the rates differ depending on different ethnic and geographically distinct populations[2]. JIA is the most common chronic rheumatic disease amongst children and is an important cause of both short and long term disability in children resulting in decreased quality of life[3]. Kenya has a high burden of infectious diseases (HIV, TB) as well as social diseases (poverty, malnutrition) which demand for a great amount of attention and resources. This has left rheumatic diseases such as JIA with limited amount of resources, education, and research. This is compounded by the fact that Kenya has very few trained paediatric subspecialists caring for children with rheumatic diseases and educating medical students and paediatric trainees. Recently Kenya appointed its first paediatric rheumatologist. There are few reports on JIA in sub-Saharan Africa. In this study, we present the spectrum and epidemiological subtypes of JIA among children seen at a rheumatology clinic in Nairobi.

Materials and Methods

This was a retrospective study carried out in the Nairobi Arthritis Clinic. The study site is situated in Nairobi, the capital city of Kenya and serves as a tertiary referral centre. It not only serves the two million inhabitants of Nairobi but also patients from all over Kenya and the greater East and Central African Region.

Following ethical approval, we reviewed the case records of all patients with a diagnosis of Juvenile Idiopathic Arthritis (arthritis in one or more joints lasting 2 weeks or more with no identifiable cause in those who are less than 16 years of age) attending the Nairobi Arthritis Clinic between January 2009 and January 2016.

Medical records of patients who met the International League of Associations for Rheumatology (ILAR) JIA diagnostic criteria of Juvenile Idiopathic Arthritis (JIA) and had been on follow up for at least 6 months were recruited into the study. This retrospective review of the JIA case records involved reclassifying each of the patients by the ILAR diagnostic JIA criteria and then compiling respective clinical data of each patient. Clinical, haematological, immunological and other relevant findings from the history were obtained from the available records. Patients were thus categorized as systemic arthritis (Stills disease), persistent oligoarthritis (4 joints or less), polyarthritis (RF negative), polyarthritis (RF positive), psoriatic arthritis and Enthesitis Related Arthritis (ERA). The remaining two subgroups within the ILAR classification system, Extended Oligoarthritis and Undifferentiated Arthritis rely on a period of observation which for many of our patients was not possible.

Patients excluded from the study were those who had signs and symptoms of other arthritis such as acute rheumatic fever, septic arthritis, systemic inflammatory disorders (systemic lupus erythematosus, vasculitis, or dermatomyositis), malignancy, human immune deficiency virus type 1 (HIV-1) infection, or metabolic diseases were excluded from the study after careful scrutiny of the respective case records. Data were collected about number of patients of each JIA subtype, gender, age at disease onset, joints involved, presence of fever, rash and pharmacological agent used. The percentage of each JIA subtype was calculated and the age of disease onset was expressed as the mean ± standard deviation (SD); as shown in Tables 1 and 2.

The major clinical data collected were large joints involvement (knee, ankle, elbow, shoulder, and wrist) or small joints involvement and presence of uveitis during the course of the disease. The presence of fever and skin rash at diagnosis was also recorded. These clinical findings were diagnosed by a rheumatologist while uveitis was diagnosed using slit lamp examination by an ophthalmologist. Initial data at diagnosis included haemoglobin level (anaemia defined as Hb < 12mg/dL), ESR > 20 mm/hr, and positivity of Anti-Nuclear Antibodies (ANA) and Rheumatoid Factor (RF) as shown in Table 2.

Review of anti-rheumatic pharmacologic treatments used during the study period included (Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), corticosteroids (intra-articular/ systemic), methotrexate (MTX), and biologic agents) was done. Number and percentage of those who were treated with NSAIDs alone, NSAIDs and corticosteroids, NSAIDs, corticosteroids and MTX, NSAIDs and NSAIDS, corticosteroids, MTX and biologics in each JIA subtype were calculated and presented in Figure 1.

Results

The records of 73 patients were reviewed of which 5 patients were excluded due to insufficient data. Table 1 shows general characteristics of the patients: Of the total 68 patients recruited, female gender was predominant in all categories of JIA apart from enthesitis related arthritis. The overall female to male ratio was 2.4:1. The range of age at onset of symptoms was between 2 years and 15 years with a mean age of 8.45 ± 4.37 years. The mean age of presentation at the clinic was 10.22 ± 3.79 years. Polyarticular rheumatoid factor negative arthritis was most common at 38.2%, followed by oligoarticular 23.5%, polyarticular rheumatoid factor positive 17.6%, systemic JIA at 14.7% and enthesitis associated arthritis at 5.9%.

Table 2 shows main clinical features of our patients; The main symptoms were in the large joints (85.2%) and fever (73.5%). The numbers of affected patients' small joints were lower at 44%. One patient had the Still's rash and another had uveitis. The ESR was raised in all categories of JIA with a mean of 44.35mm/hr while the haemoglobin was reduced with a mean of 10.82mg/dl. Ferritin levels were elevated in 11.8% of the total population (systemic JIA at 40%, oligoarticular arthritis at 40%). Positive Rheumatoid Factor was found only in RF positive polyarticular JIA. ANA was positive in 5 out of the 46 (10.9%) samples tested (oligoarticular arthritis 2, polyarticular arthritis RF positive at 3).

Figure 1 shows the anti- rheumatic pharmacologic treatment received by our patients during the course of the disease. NSAIDs were used in all the patients. NSAIDS were combined with corticosteroids in 38/68 (55.9%) patients while NSAIDs, corticosteroids and methotrexate were used in 16/68 (23.5%) patients and biologics were received by 6/68 (8.8%) patients at different and varying length of time. Biologics used included etanercept (Enbrel), rituximab (Mabthera), and tocilizumab (Actemra).

Table 1: Profiles of JIA patients presenting at the Nairobi Arthritis Clinic

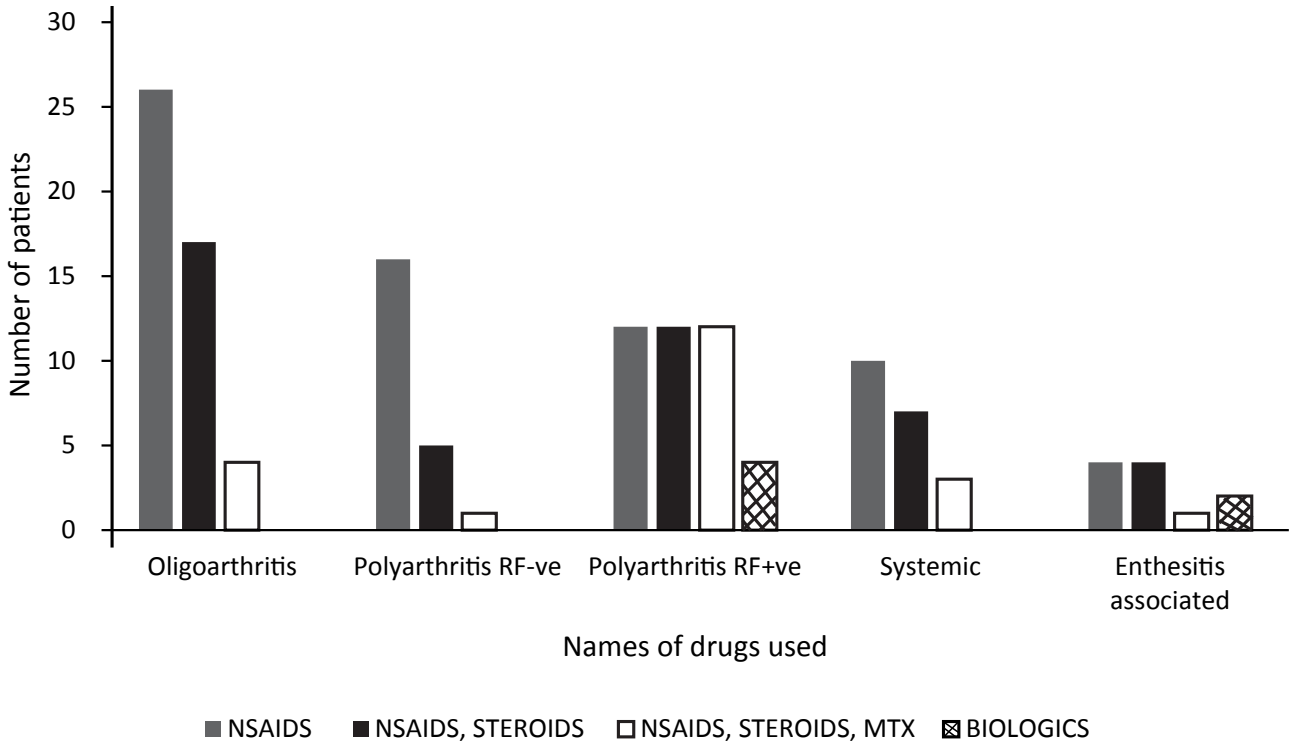
JIA subtypes	Total number	Gender M:F ratio	Age range at presentation (years)	Mean age of onset of disease (years)
Overall	68	1:2.4	2-15	8.45 ± 4.37
Systemic JIA	10 (14.7%)	3:7	3-15	8.5 ± 3.98
Oligoarticular arthritis	16 (23.5%)	1:3	2-15	6.46 ± 4.46
Polyarticular RF⁻(−) JIA	26 (38.2%)	5:8	6-15	10.7 ± 2.57
Polyarticular RF⁻(+) JIA	12 (17.6%)	0:12	6-15	10.41 ± 3.02
Psoriatic arthritis JIA	0	N/A	N/A	N/A
Enthesitis related arthritis	4 (5.9%)	3:1	10-15	12 ± 2.16
Other	0	N/A	N/A	N/A

Table 2: Clinical features related to disease categories in children with JIA

Features	Systemic JIA (n=10)	Polyarticular RF(−) JIA (n=26)	Polyarticular RF(+) JIA (n=12)	Oligoarticular arthritis (n=16)	Psoriatic arthritis JIA	Enthesitis related arthritis (n=4)	Total
ESR (mean)mm/hr	40.6±13.8	49.92±13.17	58.44±15.8	35.5±12.37	0	46.75±6.38	44.35
Percentage with elevated Ferritin	40%	0%	0%	40%	0	0	8(11.8%)
HB (mean in mg/dl)	11.0±1.86	10.01±2.01	11,54±1.2	11.3±1.46	0	11.89±1.76	10.82
Fever(n)	8	9	12	17	0	4	50(73.5%)
Large joint(n)	6	16	11	21	0	4	58(85.2%)
Small joints (n)	3	9	8	10	0	2	30(44%)
Eye involvement(n)	0	0	2	0	0	1	3 (4.1%)
Still's rash(n)	1	0	0	0	0	0	1 (1.5%)

ESR = Erythrocyte Sedimentation Rate
Large joint = knee, hip, sacroiliac, lumbar
Small joint = elbow, finger, ankles, toe, wrist

Figure 1: Pharmacologic therapy used in JIA patients



NSAIDS = Non-steroidal anti-inflammatory drugs; MTX = methotrexate; Biologics = Biologic Disease-modifying antirheumatic drugs

Discussion

This study covered a total period of 8 years and has yielded 68 cases of JIA. Table 3 is a summary of other studies that have used the ILAR classification criteria. It highlights similarities and differences between various populations worldwide in particular developed and developing countries. Similarities include a female predominance over all the JIA subtypes apart from ERA. This is in keeping with known literature that JIA is more common in females than males[4 - 7]. However the gender ratios also show a relative paucity of females in developing nations compared to studies in industrialized nations where the FM ratio is around of 5.1.

The mean age at onset of JIA was 8.45 ± 4.37 years which is largely similar to studies from Zambia and South Africa and higher than most studies from Europe, some Asian and Latin America countries[8-12]. The study noted a delay in presentation of the patients as the mean age at presentation was 10.22 years. Similar observations have been noted in other studies around Africa and Asia. This differs from data in the western world where time between age of onset to presentation was shorter[8-9,11-14] . Possible reasons for this could be that of late presentations at the clinic due to late referrals after the onset of the initial symptoms, cultural stigma surrounding JIA and socioeconomic reasons. This is an area for future studies.

The predominant subtype of JIA was the polyarticular arthritis rheumatoid factor negative arthritis was most common at 38.2%. This differs with most studies where oligoarticular arthritis is the most common[4 - 8]. This is likely due partially at least to the low prevalence of oligoarticular arthritis observed in studies from Africa and India as compared to Western cohorts. Young preschool females predominate in this particular subset in European and UK studies[7]. It has been described in the literature that non-European populations have a decreased relative risk of suffering from oligoarthritis[15]. Since our study was undertaken in a tertiary center, we believe that selection bias may have contributed to the lower numbers of oligoarticular arthritis. Milder forms of JIA especially oligoarticular may be treated by general paediatricians or orthopaedic doctors and end up not being referred to a secondary care facility[10,13,16]. It is possible therefore that some children classified as polyarticular may in reality be "oligoarthritis extended". In this context it is of interest that in true community based studies in the developing world the prevalence of oligo articular disease matches or exceeds that of polyarticular disease[16].

The relatively high prevalence of the rheumatoid factor positive group in our study and three other Africa studies to date [9,10,17], seems to support the notion that Africans are at an increased risk for this particular type of JIA[15.] We must mention there is a limitation in getting two positive RF assays at least 3 months apart in the first 6 months of the disease in order to diagnose RF positive polyarthritis as required in the ILAR diagnostic criteria due to financial constraints[1]. As standard practice in our clinics one positive or negative assay is considered to be sufficient to classify a patient with polyarthritis. This is one of the drawbacks of using ILAR diagnostic criteria in low income resource set ups. This difficulty is mentioned in South Africa, India and a study of Nordic children[9,13,18]. Thus it is possible RF positive polyarthritis patients may be overrepresented in our polyarticular subtype thus reducing the RF negative numbers as the patients were classified using one positive assay.

Table 3: Comparative JIA epidemiology: developing and developed countries

JIA subtypes	Kenya	Zambia[8]	South Africa[7]	Morocco[9]	Egypt[12]	Oman[11]	India[13]	Turkey[10]	Saudi Arabia[14]	Latin America[6]	United Kingdom[20]
Number in the studied series	68	78	78	80	196	107	235	196	82	397	507
Female: Male Ratio	2.4:1	1.2:1	1:1	1.4:1	1.09:1	2.5:1	1:1.4	1:1.1	1.64:1	2.125:1	1.8:1
Mean age of onset	8.45	9.4	8(7.3)		6.257	6.85	12	7	7.11	6.6	6.8
Systemic JIA (%)	14.7	14.1	7.7	26	24	17.8	8	5.3	36.5	28.5	5.3
Polyarticular (%)				31.5	34.7					40.6	
Polyarticular RF (−) JIA (%)	38.2	34.6	14			39.2	17	30.6	24.39		13
Polyarticular RF (+) JIA (%)	17.6	11.5	26.9			7.5	12	6.6	4.87		2.3
Oligoarticular arthritis (%)	23.5	32.1	26	42.5	41.3	31.8	21	34.1	28.04	30.9	46
Psoriatic arthritis JIA (%)		1.3	1.3				1	1	4.87		7
Enthesitis related arthritis (%)	5.9	6.4	23			3	36	10.3	1.21		6.3

The main symptoms were large joints (85.2%) and fever (73.5%). The number of affected patients' small joints were lower at 44%. Literature shows that large joints apart from the hips are most affected as compared to small joints[4]. A higher percentage of patients with fever was reported in our cohort. The numbers with systemic JIA were low but comparable with other studies, of which 80% of these patients reported fever[9,10,14]. Picking up other extra-articular features is a challenge in our low resource set-up and Africa as a whole that is burdened by infectious disease. We found one patient with uveitis. As rheumatology knowledge increases amongst doctors and other care providers in low resource settings like Africa, leading to the application of standard diagnostic and classification criteria, prevalent cases are likely to continue to resemble those reported elsewhere. The subgroup of ERA is uncommon though follow up studies on prevalence of HLA B27 will also be required. This is similar to data from Zambia but differs from South Africa where they found large numbers with ERA[9]. However, it's important to note the South African study wasn't a pure African population.

Majority of our patients had anaemia (61.37%) with a mean haemoglobin of 10.82mg/dl. This was comparable to other studies on JIA populations[14]. Anaemia in JIA is commonly caused by iron deficiency or due to chronic inflammation[14,19]. This is higher than what is quoted in local data at 28.8%[18]. Rheumatic fever is still common in our set-up, ASOT titers were done on 14 samples, of which one turned out positive. ANA was positive in 5 out of the 46 (10.9%) samples tested (oligoarticular arthritis 3, polyarticular arthritis RF positive at 2). This is similar to other studies that found low numbers of ANA positivity [9,20]. As expected most ANA positivity cases were in oligoarticular JIA.

The goals of management of JIA are control active symptoms, achieve remission, prevent joint damage, and preserve joints function to prevent disability as well as maintaining normal growth. Pharmacologic therapy of JIA has major advances over the last two decades especially with the introduction of biologics. In low resource setups like ours, patients have difficulties accessing these rheumatic drugs let alone biologics mainly due to costs and their availability. Another stumbling block is the lack of local clear guidelines on diagnosis and management of common rheumatic conditions including JIA. Our practice is to start with NSAIDs for 4 to 6 weeks followed by DMARDs, most commonly methotrexate in case of no adequate response to NSAIDs. IAC are used to relieve joint inflammation and systemic steroids are usually used for a short time with the lowest effective dose and are tapered once we get the desired response. In case of failure of methotrexate, the options include trial of another DMARD or biologic therapy is introduced. NSAIDs were used in all the patients. NSAIDS were combined with corticosteroids in 55.9% patients while NSAIDs, corticosteroids and methotrexate were used in 23.5% patients and biologics were received by 6 patients at different and varying length of time. Biologics used included etanercept (Enbrel), rituximab (Mabthera), and tocilizumab (Actemra). It's important to note a number of patients met the criteria for biologics but due to costs were not started on them.

A major limitation of our study is being a retrospective record-based in nature and a single center-based with a relatively small sample size. Another limitation is that the patients attending this rheumatology clinic may have more severe disease than those in the community. Milder forms of JIA have a higher chance of going into remission and may not need to be referred to a rheumatology clinic. However, our study can be a starting point to raise the awareness about JIA and possible more studies on prevalence, disease activity and its impact on the school going children nationwide. We recommend that more needs to be done to improve on diagnosis through education and diagnostic equipment and management of these patients by availing appropriate medicines. This study also suggests that there should be a modification of the ILAR diagnostic criteria to suite low income resource areas.

Conclusion

This is the first JIA study done in Kenya. JIA in this study population has similarities and differences with profiles compared to other international JIA studies. It shares characteristics with other studies that it is predominantly female, affects large joints with polyarticular arthritis subtype being the most common form in our population. There are difficulties with the ILAR classification in our setting, specifically regarding the requirement of 2 rheumatoid factor tests. The subgroup of ERA is uncommon though follow up studies on prevalence of HLA B27 will also be required. The most common presentation of a JIA patient in our set-up is fever, affects large joints and anaemia. The most common form of pharmacological interventions is NSAIDS and corticosteroids. The use of biologics in this set up is still very low. Late presentation coupled with the absence of specialized health services are issues that will need to be addressed.

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Conflict of interest

The authors declare no conflict of interest.

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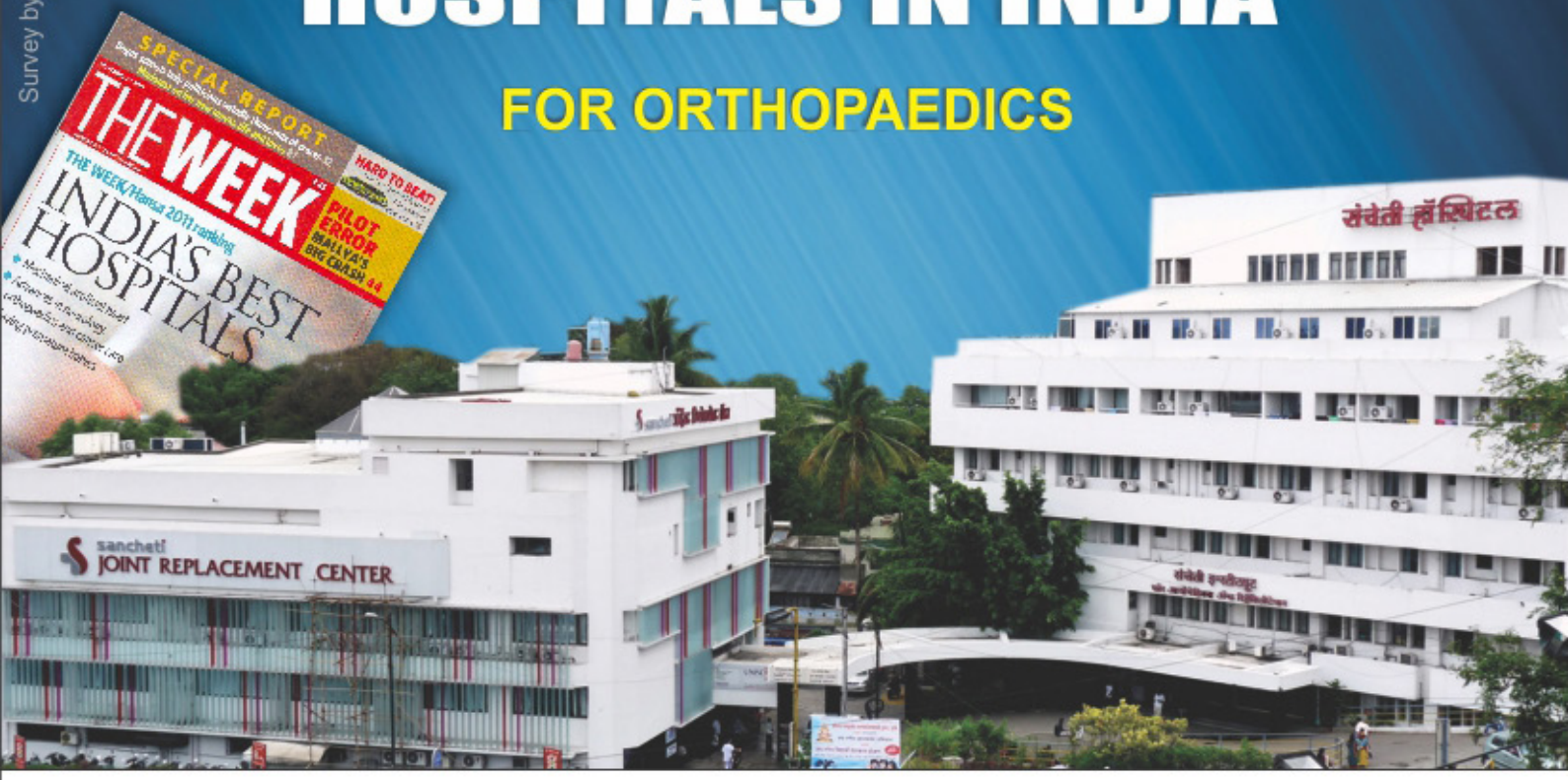

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