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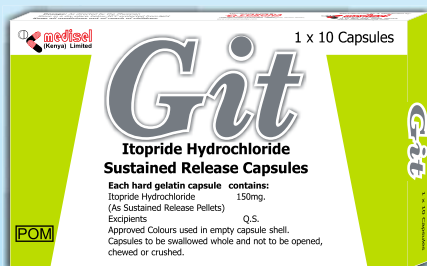
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Otieno FO

*Faculty of Internal Medicine,
Aga Khan University,
Nairobi, Kenya
Email: fred.otieno@aku.edu*

Fibromyalgia or Fibromyalgia Syndrome (FMS) is a complex chronic pain disorder of unknown causation frequently associated with debilitating fatigue, unrefreshing sleep, cognitive and affective symptoms. Analogous symptomatic conditions have been medically recognized since the early 1900s, when initially labeled as “fibrositis”. Since the early 1980s, FMS has evolved and differentiated after its characterization in a controlled study. Since then, research has focused on multiple aspects of this disorder, including characterization and management of symptoms, psychophysiology, neuroendocrine-immune pathophysiology, including central sensitization mechanisms¹.

In addition to chronic pain, patients with FMS report a number of somatic and cognitive difficulties. These include mood disorders, persistent fatigue, cognitive dysfunction, headaches, irritable bowel syndrome, and insomnia. FMS, therefore, can be conceptualized as an entity with abnormalities spanning a range of symptom domains – cognition, fatigue, mood, anxiety and sleep. This diversity of symptom presentation poses a challenge as to which doctors should primarily take care of FMS patients. However, while FMS patients are not usually immediately referred to rheumatologists, many rheumatologists see enough FMS patients to acquire experience in the subject. The combination of experience treating chronic pain conditions and treating FMS patients specifically often means that rheumatologists offer valuable expertise when it comes to treating FMS.

Are most rheumatologists comfortable treating patients with FMS, especially in set ups where there is little or non-existent multi-disciplinary teams? Several surveys have been conducted amongst rheumatologists about this topic. Very interesting and varied opinions about the disease have arisen. Some rheumatologists have described FMS as a ‘nightmare consultation’ with some even

questioning the existence of the condition as a disease entity! Many see FMS as a symptom description that is slowly evolving into a spurious diagnosis! With such a wide range of opinion, it is likely that patients with fibromyalgia are receiving different levels of support, advice and treatment!

The big question thus is “How can prejudice and skepticism regarding the validity of fibromyalgia be countered?” Knowledge that FMS is grounded in neurophysiological mechanisms will reduce skepticism regarding a syndrome of subjective complaints. Rheumatologists comfort with a biomedical paradigm, which prioritizes diagnostics, adds to the insecurity in management of these patients, with some authors contending that the label of FMS promotes poor health^{2,3}. Patient preoccupation with physical symptoms rather than developing control over illness invokes frustration for the healthcare professional and erodes a good therapeutic relationship⁴. The construct of somatization has however never been validated in situations involving pain, and particularly in FMS. In contrast, patients with FMS report frustration with healthcare professionals, dissatisfaction with the clinic visit and seek a concrete somatic diagnosis^{5,6}. Although discordance between patient and physician assessment of health perceptions has been reported, rheumatologists have expressed the desire to comply with patients’ wishes and avoid frustration⁷. When rheumatologists prejudge FMS patients in moralizing terms and believe them to be illness-focused, demanding and medicalized, the patient doctor alliance will be eroded with adverse effect on patient outcome⁵. Both the individual patient’s concept of illness as well as perceived attitudes of the healthcare team influences global well-being. Shared decision-making between patient and physician can improve the

quality of interaction⁷. An early diagnosis may have pharmacoeconomic implications with reduced healthcare costs as measured by fewer investigations, less referral to specialists and reduced healthcare visits ^{6,7}.

Whereas opinion is highly divided amongst rheumatologists as to the approach of patients with FMS, it is my opinion that holistic management of FMS patients is a very useful concept, which allows the clinician to promote beneficial lifestyle changes to patients who appear to have lost their 'pain filter', and who would otherwise resist such initiatives. The complex and multifaceted nature of FMS lends itself better to a holistic (integrative medicine) or biopsychosocial approach than the more specific bio-scientific pathways typical for a pathologically defined disease. A person-centered approach to evaluation and care more effectively addresses and encompasses the biopsychosocial aspects of this disorder than traditional bio-scientific clinical methods. Rheumatologists should not shy away from forming multi-disciplinary teams with other colleagues e.g. psychiatrists, counselors, neurologists, nurses, pain management specialists etc.

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Kubo MN¹, Oyoo GO²

¹Unit of Clinical Pharmacology, Department of Clinical Medicine and Therapeutics, University of Nairobi, Kenya

²Associate Professor of Rheumatology, Department of Clinical Medicine and Therapeutics, University of Nairobi, Kenya

Corresponding author:
Dr Mary N Kubo. Unit of Clinical Pharmacology, Department of Clinical Medicine and Therapeutics, University of Nairobi, P.O. Box 19676-00202, Nairobi, Kenya.
Email: nigandimarie@gmail.com

Abstract

Objective: To review current and emerging pharmacologic treatment options for gout, with particular emphasis on the rapidly changing recommendations outlined in the latest treat to target strategy employed in the 2016 European League Against Rheumatism (EULAR) guidelines.

Data source and extraction: Published clinical drug trials, reviews and guidelines for the treatment of gout. Research work published in English and emphasizing pharmacologic management of gout was included after online and library searches.

Conclusion: Research into pharmacologic therapies for gout had largely remained silent after licensing of allopurinol in 1966. Since 2008 however, with approval of febuxostat and pegloticase, the stage has been set for exciting research into new molecules in the management of this largely curable condition. Updated evidence supporting the use of current and emerging agents such as febuxostat, canakinumab, lesinurad and pegloticase is summarized in this review.

Key words: Gout; Acute flare therapy, Urate lowering drugs

Introduction

Recent advances in therapy for gout provide exciting new possibilities in reduction of gout-associated morbidity and disability. With a prevalence of up to 2-4%¹, gout is a common and disabling condition that remains poorly managed. Unlike rheumatoid arthritis, premature mortality associated with gout has remained unimproved over the last decade².

Gouty arthritis is a result of deposition of monosodium urate crystals within tissue, with resultant inflammation and joint destruction. Elevated serum uric acid levels contribute to this pathophysiology, either as a result of increased production or reduced renal excretion of urate. Various co-morbid conditions associated with gouty arthritis further complicate its management, with

drug interactions commonly encountered when treating patients with concomitant hypertension, diabetes, chronic kidney disease, cardiovascular disease and dyslipidemia³.

Pharmacologic therapy targets a reduction in uric acid levels, as well as control of inflammation present during acute flares. This review looks at current and emerging therapeutic options available for gout management, in line with the latest treat-to-target strategy recommended by the European League Against Rheumatism (EULAR) and the British Society for Rheumatology^{4,5}.

Acute flares

Pathogenesis of acute gouty arthritis

Uric acid crystals deposited within the joint cavity are engulfed by synovial phagocytic cells, triggering release of lysosomal enzymes and inflammatory cytokines. Monocytes produce TNF, IL-1, IL-6 and IL-8, while mast cells produce histamine and IL-1, with resultant increased vascular permeability and vasodilatation. Increased IL-8 in phagocytes leads to activation of neutrophils, further exacerbating the inflammatory response.

Pharmacologic management of acute flares is most efficient when begun early after flare onset, and includes use of colchicine, Non Steroidal Anti-Inflammatory Drugs (NSAIDs), steroids, and, recently, IL-1 antagonists such as canakinumab.

Colchicine

A first line agent used in management of acute gouty flares, colchicine achieves its antiinflammatory effect via various mechanisms. It concentrates within leukocytes, disrupting microtubule polymerization and inflammasome function, interfering with neutrophil chemotaxis, adhesion, recruitment and superoxide production. Additionally, colchicine inhibits release of IL-1 and 8⁶.

Of note, colchicine has a narrow therapeutic window and potential for life threatening drug interactions. Its most common adverse effects include

abdominal pain, nausea, diarrhoea, pharyngolaryngeal pain and blood dyscrasias. GIT adverse effects are usually the first signs of colchicine toxicity and should lead to prompt dose reduction or discontinuation of the drug.

Recent evidence from the AGREE Trial (Acute Gout Flare Receiving Colchicine Analysis) showed that when taken within 12 hours of symptom onset, lower doses of colchicine at 1.8mg (1.2mg then 0.6mg one hour later, self-administered) were as effective and better tolerated than traditional higher doses of 4.8mg⁷. Colchicine is available in 1mg and 0.5mg tablets, therefore recommended dosage is 1mg followed an hour later by 0.5mg, as per the EULAR guidelines⁴. Patient education on self-medication is key to halt flares early, thus physicians are further encouraged to adopt the 'pill in the pocket' approach in fully informed patients.

Colchicine is a substrate for intestinal and hepatic CYP3A4, as well as the P-glycoprotein 1 reflux transporter. Fatal drug interactions have been reported when colchicine is used concomitantly with P-glycoprotein inhibitors such as cyclosporine, verapamil and ranolazine, as well as CYP3A4 inhibitors including clarithromycin, itraconazole, ketoconazole and some protease inhibitors. In addition, myopathy and rhabdomyolysis have occurred when concomitantly used with statins, fenofibrate, gemfibrozil and digoxin⁶.

Excretion of colchicine is predominantly via the hepatobiliary route, thus dose should be reduced in patients with hepatic impairment. About 10-20% of colchicine is cleared through the kidneys, hence will accumulate in patients with impaired renal function. Dose should be limited to 0.5-0.6mg/day in moderate renal insufficiency (eGFR 30-60 mL/min) and 0.5-0.6 mg every 2 to 3 days if eGFR is 15 to 29mL/min. It is contraindicated in stage 5 chronic kidney disease (eGFR<15mL/min or dialysis)⁸.

Apart from its anti-inflammatory effect in acute gouty arthritis, colchicine may have additional beneficial effects in reduction of cardiovascular risk, which is increased in patients with gout and hyperuricemia^{9,10}. Emerging evidence from recent trials increasingly points towards a possible role of colchicine in reduction of adverse cardiovascular outcomes in patients with gout^{11,12}.

Non Steroidal Anti-inflammatory Drugs (NSAIDs)

NSAIDs have long been a mainstay of acute gouty flare management, acting via inhibition of cyclooxygenase enzymes, thus reducing production of prostaglandins that mediate pain and inflammation. Indomethacin was the first NSAID used in acute flare treatment¹³, and although it has demonstrable efficacy, side effects including headache, nausea and vertigo limit its use¹⁴. Other traditional NSAIDs, though efficacious, are usually poorly tolerated due to a high incidence of dyspepsia, peptic ulceration, and GI bleeding, prompting the use of concomitant proton pump inhibitor therapy. Indomethacin is considered one of the more GI toxic traditional NSAIDs¹⁵.

Newer COX-2 selective agents may be preferred, due to their selective inhibition of inducible COX-

2 that mediates prostaglandin production mainly at sites of inflammation, sparing the constitutive COX-1 responsible for GI tract mucosal integrity. Several trials have confirmed comparable efficacy and better tolerability of celecoxib (200mg to 400mg twice a day) and etoricoxib (120mg once a day) in control of acute gouty flares compared to traditional NSAIDs^{16,17}.

Lumiracoxib is a novel COX-2 inhibitor with proven efficacy and good tolerability in treatment of chronic pain in osteoarthritis from the TARGET study (Therapeutic Arthritis Research and Gastrointestinal Event Trial)¹⁸. Lumiracoxib 400mg once a day reduced incidence of serious GI complications by 79% compared to traditional NSAIDs. Additionally, a randomized control trial of lumiracoxib 400mg once a day in acute gout showed comparable anti-inflammatory efficacy to indomethacin, less GI adverse effects, and an additional benefit of reduction of blood pressure levels compared to traditional NSAIDs¹⁹. NSAIDs should be prescribed for a total of 5 to 10 days, or until symptoms resolve.

Steroids

An alternative to NSAIDs and colchicine in acute gouty flares, steroids such as prednisone are surprisingly prescribed only about 9% of the time for management of acute gout in the US²⁰. Evidence from several randomized trials comparing steroids and NSAIDs in acute gout consistently shows similar efficacy of prednisone 30-35mg once a day for five days when compared to NSAIDs such as indomethacin or naproxen^{21,22}.

Concerns regarding the adverse effect profile of steroids may contribute to the low prescription rates of these agents. No significant adverse effects were encountered with short term oral steroid use in gout^{21,22} as well as rheumatoid arthritis²³. In addition, steroids are a safe alternative in patients with contraindications to NSAID and/or colchicine use, eg patients with significant renal impairment. They should however be avoided in patients with concomitant infection, brittle diabetes or postoperatively due to impaired wound healing. Prednisolone is the steroid of choice in patients with hepatic impairment, since prednisone requires conversion to the active prednisolone form in the liver.

Despite lack of randomised trials to support use of intraarticular glucocorticoid injections²⁴, two small studies^{25,26} and EULAR guidelines⁴ consider that this may be an option in select patients with monoarthritis of an easily accessible joint. Options include triamcinolone acetate 40mg for a large joint (eg. knee), 30mg for a medium joint (eg. wrist, ankle, elbow), and 10mg for a small joint. 40 to 80 mg of intraarticular methylprednisolone may also be used²⁷.

Interleukin 1 antagonists

Interleukin 1 β , a proinflammatory cytokine whose release is triggered by monosodium urate crystals, plays an integral role in gouty arthritis inflammation. Canakinumab is an anti IL-1 β monoclonal antibody with

a long half life of 3 to 4 weeks, that has been approved in Europe for management of acute gouty flares in patients with contraindications, intolerance or non-response to colchicine, NSAIDs or steroids⁴.

Evidence from randomized trials including β -RELIEVED and β -RELIEVED-II showed that one dose of subcutaneous canakinumab 150mg was superior to triamcinolone in pain reduction in acute flares as well as prevention of episodes of re-flare²⁸. Of particular concern with use of anticytokines is their potent immunosuppressant effect that may increase the risk of serious infections and malignancy. In these studies rates of infection were increased in the canakinumab group, which resolved with standard of care. No opportunistic infections were reported, and only one benign neoplasm (lipoma) was noted²⁸. Screening for occult infections is recommended prior to initiation of anticytokines such as canakinumab.

Anakinra, an interleukin 1 receptor antagonist, has also shown promise in management of acute gouty arthritis. Subcutaneous anakinra at a dose of 100mg for 3 days was shown to reduce pain in patients with acute gout²⁹. On the other hand, rilonacept, a soluble IL-1 α and IL-1 β receptor fusion binding protein showed no benefit in pain relief over indomethacin³⁰.

Role of combination therapy in acute flares

In patients with particularly severe flares of gout involving multiple joints, EULAR guidelines recognize the need for combination therapy using colchicine plus either an NSAID or steroids⁴.

Urate Lowering Therapy (ULT)

Unlike previously where Urate Lowering Therapy (ULT) was reserved for patients with recurrent acute gout attacks, presence of tophi, urolithiasis or urate overproduction, ULT should now be considered from the first presentation of gout, particularly for patients with comorbidities (eg. hypertension, ischaemic heart disease, chronic kidney disease) and/or serum uric acid >8mg/dL (480 μ mol/L). Target serum uric acid level should be <6mg/dL (360 μ mol/L) and <5mg/dL (300 μ mol/L) in those with severe gout⁴. Severe gout is characterized by presence of tophi, chronic arthropathy and/or frequent acute attacks (>2 per year).

Urate lowering therapies are key to achievement of gout cure. Lowering serum urate concentrations below the saturation point of monosodium urate (6.8mg/dL) leads to dissolution of existing monosodium urate crystals and retards new crystal formation, preventing further attacks of gout and joint damage. ULT also reduces the size and number of tophi, and improves patient quality of life.

Of note however is that as the serum uric acid levels fall, there is mobilization of uric deposits from tissues, leading to flares of acute gout in the initial weeks to months after initiation of urate lowering therapy. Prophylaxis against such flares should thus be initiated using low-dose colchicine (0.6mg/day) or naproxen

(250mg twice a day) for up to 6 months, rather than 8 weeks as previously recommended^{4,31}. Emerging evidence also points towards a combination of patient education and slow upward titration of urate lowering therapy (specifically allopurinol) possibly obviating the need for flare prophylaxis³².

Urate lowering therapy should be initiated at least two weeks after resolution of an acute attack, although two small trials have pointed towards minimal risk of worsened or prolonged flares with immediate (during flare) versus delayed (after two weeks) allopurinol initiation^{33,34}. ULT should be started at a low dose and titrated upwards, with a goal of lifelong maintenance of serum uric acid at less than 6mg/dL (360 μ mol/L). Urate lowering therapies include xanthine oxidase inhibitors, uricosuric agents and recombinant urate oxidases.

Xanthine oxidase inhibitors

Xanthine oxidase is an integral enzyme in human purine metabolism. It is responsible for oxidation of hypoxanthine and xanthine, with subsequent production of uric acid. Inhibition of this enzyme by allopurinol and febuxostat allows uric acid lowering to target levels.

Allopurinol

A structural isomer of hypoxanthine, allopurinol is a purine analog that is the recommended first line urate lowering agent in patients with gout and normal kidney function⁴. It is rapidly converted to its active metabolite, oxypurinol, by xanthine oxidase. Oxypurinol is excreted mainly via the kidneys, thus accumulating in patients with renal impairment. Increased body weight and use of diuretics will increase dose requirements of allopurinol³⁵.

Whereas the half life of allopurinol is 1 to 2 hours, oxypurinol has a relatively longer half life of about 15 hours, allowing once daily dosing. Recommended starting dose is 100mg/day, uptitrated every two to four weeks to a maximum dose of 800 to 900mg/day. It should be noted that the commonly used standard dose of 300mg/day failed to achieve target serum uric acid levels in upto 50% of patients with normal kidney function³⁶, thus uptitration of its dose should be considered for maximal benefit.

Allopurinol should be started at a low dose to reduce risk of Serious Cutaneous Drug Reactions (SCARs) including toxic epidermolysis/Steven Johnson syndrome and Drug Related Eosinophilia with Systemic Symptoms (DRESS) syndrome. Carriers of the HLA*B5801 allele are at higher risk of these cutaneous manifestations. Additionally, patients with impaired renal function are at higher risk of SCARs, thus allopurinol dose should be adjusted according to creatinine clearance. Although rare, allopurinol-associated SCARs carry a high mortality rate of 25-30%³⁷.

In patients who do not achieve target serum uric acid levels despite allopurinol dose adjustment, one can switch to febuxostat or a uricosuric, or allopurinol can be combined with a uricosuric agent⁴.

Febuxostat

A nonpurine xanthine oxidase inhibitor, febuxostat is eliminated predominantly via hepatic pathways, thus can be used in patients with mild to moderate renal failure. Several randomized controlled studies^{38,39} have shown superior urate lowering efficacy of febuxostat 80mg or 120mg compared to standard dose allopurinol at 300mg. Incidence of adverse effects was similar across all groups. It should however be noted that allopurinol dose was not titrated upwards to maximal doses in these trials.

The febuxostat versus Allopurinol Controlled Trial (FACT) further highlights the importance of flare prophylaxis using colchicine or low dose naproxen for a prolonged duration³⁸. Prophylaxis in this study was only given for eight weeks, with a high rate of gout flare in all treatment groups on withdrawal of prophylaxis. Febuxostat does not need to be discontinued if a flare occurs. Additionally, low dose febuxostat at 40mg was shown to be non-inferior to allopurinol 300mg in the CONFIRMS trial³⁹.

Liver function tests should be monitored in patients on febuxostat as it may cause abnormalities in liver function. Other adverse effects include nausea, arthralgia and cutaneous reactions. It exhibits no cross sensitivity with allopurinol. Like allopurinol, febuxostat may increase levels of theophylline, mercaptopurine and azathioprine, resulting in toxic levels of these drugs.

There have been concerns raised regarding adverse cardiovascular outcomes in patients on febuxostat³⁹. The recently published CARES trial (Cardiovascular Safety of Febuxostat or Allopurinol in patients with gout) compared cardiovascular outcomes in over 6,000 patients with gout and coexisting cardiovascular disease, who were on either febuxostat or allopurinol⁴⁰. There was no difference in the rates of major adverse cardiovascular events between the two groups, which was the primary end point. However in the analysis of secondary end points, risk of cardiovascular mortality was higher in the febuxostat group (HR 1.49, 95% CI 1.01 - 2.22). The study was carried out on patients at high risk of cardiovascular mortality due to pre-existing major cardiovascular disease, and results may not be generalizable to patients without coexistent cardiovascular disease. Febuxostat should however be prescribed with caution in patients with history of cardiovascular disease.

Uricosuric agents

Since impaired renal excretion of urate is a significant contributor to increased serum uric acid levels, uricosuric agents continue to play an important role in management of gout. About 90% of filtered urate is reabsorbed in the kidneys via urate transporters such as uric acid transporter 1, glucose transporter 9 and organic anion transporters 1, 3 and 4. These are the targets for the uricosuric agents probenecid, benzbromarone and the novel agent lesinurad.

Uricosuric agents are recommended alone (except for lesinurad) or in combination with allopurinol in patients unable to achieve serum uric acid target levels with maximal doses of allopurinol. They may precipitate urate stones in the kidney and patients should be advised to have high fluid intake to prevent urolithiasis.

Probenecid

An organic anion transporter inhibitor, probenecid was the first commercialized urate lowering drug. It is started at a dose of 250mg twice daily, increased weekly up to 1g twice a day. In patients without proper control on allopurinol 300mg/day, 65% of patients reached target serum uric acid levels when switched to probenecid 2g daily³⁶. Further, a combination of allopurinol-probenecid was more effective than allopurinol alone in lowering serum uric acid⁴¹.

Adverse effects associated with use of probenecid include renal calculi, gastrointestinal intolerance and skin rash. Concomitant use with allopurinol prolongs the half life of probenecid. Excretion of penicillin, NSAIDs and methotrexate is reduced when administered together with probenecid.

Benzbromarone

A more potent uricosuric agent compared to probenecid, benzbromarone achieves its urate lowering effect via an active metabolite, 6 hydroxybenzbromarone. This metabolite inhibits renal urate reabsorption via inhibition of urate transporter 1 (URAT1). Initially licensed for use in the 1970's, benzbromarone was withdrawn in 2003 after reports of serious hepatotoxicity, but is still available in some countries outside of the US (eg in Europe and Southeast Asia)⁴².

It is one of the uricosuric agents recommended in the EULAR guidelines for management of gout, either alone or in combination with allopurinol⁴, at a dose of 50-200mg/day. In patients unable to achieve adequate urate lowering with allopurinol 300 mg, upto 92% were able to reach target serum uric acid levels when switched to benzbromarone 200mg³⁶. Benzbromarone can be used in patients with moderate renal impairment, but is not recommended once the eGFR falls below 30mL/min.

Lesinurad

A novel Selective Uric Acid Reabsorption Inhibitor (SURI), lesinurad achieves its uricosuric effect via inhibition of renal urate transporter 1 (URAT1). Lesinurad 200mg was approved (in combination with xanthine oxidase inhibitors) for therapy of gout by the US Food and Drug Administration as well as the European Medicines Agency in 2015.

At doses of 200mg and 400mg, lesinurad showed superior urate lowering effect when combined with allopurinol in the phase III multinational CLEAR-2 study (Combining Lesinurad with Allopurinol Standard of

Care in Inadequate Responders), compared to allopurinol alone⁴³. These findings were further mirrored when lesinurad was combined with febuxostat⁴⁴.

Though more efficacious in urate level reduction, the higher 400mg lesinurad dose was associated with more adverse effects, including a reversible elevation in serum creatinine levels. Notably, there was no increased risk of urolithiasis seen in the CLEAR-2 study, perhaps due to the fact that concomitant allopurinol use reduces uric acid production. Additionally, lesinurad was prescribed as a once daily dose in the morning, a time when the potential for uric acid precipitation is lowest due to high urine volume and urine pH.

Arhalofenate

A novel uricosuric agent, arhalofenate is the first agent to have both urate lowering and anti-flare effects. It reduces uric acid reabsorption in the proximal tubules via inhibition of uric acid transporter 1 (URAT1). Additionally, in murine models, it had anti-inflammatory activity through suppressed release of proinflammatory cytokines such as Interleukin 1 β , a key cytokine in promoting gout flares⁴⁵.

In a phase IIb clinical trial, arhalofenate 800mg decreased gout flares significantly compared to placebo, and had no significant difference in reduction of gout flares when compared to allopurinol plus colchicine⁴⁶. It additionally decreased serum uric acid levels by 16%, with a favourable safety profile. Arhalofenate as an oral, once daily fixed dose combination with febuxostat is currently in phase III clinical trials.

Urate oxidases

In most mammals, uric acid is metabolized by uricase enzyme to the more soluble allantoin that is readily excreted by the kidneys. Mutational inactivation of this enzyme in humans occurred in the Miocene era (5-23 million years ago), possibly to maintain an evolutionary advantage associated with antioxidant properties of high levels of serum uric acid.

Rasburicase, a recombinant fungal urate oxidase, was the first recombinant uricase developed for management of tumour lysis syndrome in children. It has however not been licensed for use in gout, due to its short half life and high immunogenicity.

Pegloticase

Produced by a genetically modified strain of *Escherichia coli*, pegloticase is a recombinant uricase that is covalently conjugated to monomethoxypoly(ethylene glycol). This conjugation reduces its immunogenicity and increases its solubility as well as serum half life to approximately 2 weeks⁴⁷. It is administered intravenously and remains in circulation, degrading uric acid and resulting in a urate concentration gradient that draws further uric acid from tissues.

Pegloticase is highly effective, dramatically reducing serum uric acid levels to as low as 1mg/dl within 24-72 hours⁴⁸. It is FDA approved at a dose of 8mg every

two weeks in patients with refractory gout, defined as clinically severe crystal-proven gout not properly treated with conventional urate lowering therapy, including a combination of a xanthine oxidase inhibitor and a uricosuric agent⁴. In addition to urate lowering effect, pegloticase use also leads to more rapid resolution of tophi compared to conventional urate lowering therapy⁴⁷.

Whereas pegloticase is highly effective in lowering uric acid levels in some patients, there exists a small subset of patients who are either partial responders, or non-responders. This is due to generation of antipegloticase antibodies (titres typically above 1:2340), leading to loss of response after a mean period of about 6 weeks of therapy⁴⁹. These antibodies may occur in upto 40% of patients, resulting in increased drug clearance, sub-therapeutic drug levels, and higher risk of infusion reactions⁴⁹. Serum uric acid levels should be measured in the 24 hours preceding reinfusion, and the drug stopped if uricemia is not decreased. Importantly, no other urate lowering drug should be prescribed concomitantly so as to maintain this warning signal⁸.

Probably due to its rapid lowering of serum uric acid levels, the most common adverse effect associated with pegloticase is gout flare, occurring in upto 70% of patients, despite flare prophylaxis with colchicine or NSAIDs⁴⁷. Additionally, infusion reactions, anaphylaxis and haemolysis in patients with glucose-6-phosphate dehydrogenase deficiency may occur.

Other agents with urate lowering effect

Losartan

An angiotensin II receptor blocker used in hypertensive patients, losartan has been shown to have a probenecid-like uricosuric effect due to its high affinity for, and inhibition of the urate transporter URAT1⁵⁰. Its urate lowering effect approaches 20-25%⁵⁰, and appears to be unrelated to angiotensin II receptor blockade, as other drugs in this class do not have a similar effect on uric acid levels. It thus presents a useful pharmacologic tool in hypertensive patients with comorbid gout.

Calcium channel blockers

Due to their effect on increasing glomerular filtration rate, calcium channel blockers may consequently enhance renal clearance of uric acid. Specifically, nifedipine⁵¹ and amlodipine⁵² have been shown to reduce serum uric acid levels, with a consequent reduction in risk of gout by 13% and 21% respectively⁵⁰.

Statins and fenofibrate

Primarily useful for their lipid lowering effect, statins and fenofibrate have additional beneficial effects on uric acid levels. Fenofibrate lowers serum uric acid by upto 20%, via an increase in renal uric acid excretion⁵³. Statins exhibit a more modest serum uric acid reduction of between 3% (rosuvastatin) and 6.5% (atorvastatin)⁵⁴.

Canagliflozin

A sodium-glucose co-transporter 2 inhibitor used for management of diabetes mellitus, canagliflozin reduced serum uric acid levels to <6mg/dl in 20-30% of type 2 diabetic patients with concomitant hyperuricemia⁵⁵. A postulated mechanism of its urate lowering effect may involve the renal GLUT9 transporter that exchanges glucose for uric acid. Due to higher glucose concentration in urine with canagliflozin treatment, GLUT9 may release more uric acid into the urine in exchange for glucose.

Future directions in pharmacologic therapies for gout

With robust research into newer molecules ongoing, physicians can look forward to possibly more efficacious agents in the near future. These include single agents with dual mechanism of action targeting both xanthine oxidase and renal urate handling, newer xanthine oxidase inhibitors such as topirostat and extended release febuxostat (phase III trials), novel uricosuric agents like verinurad (phase II trials), as well as the orally administered Interleukin 1 β inhibitor bucillamine. Additionally, to improve immune tolerance, trials combining a nanoparticle-encapsulated pegsiticase (a pegylated uricase) with the immune modulator rapamycin are also underway⁵⁶.

Conclusion

With such a wide armamentarium of pharmacologic agents, clear management guidelines and a target approach, cure for a majority of gout patients is now possible. Gout need not be the chronic, debilitating disease it once was.

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Department of Clinical
Medicine and Therapeutics,
School of Medicine,
College of Health Sciences,
University of Nairobi, P. O.
Box 19676-00202, Nairobi,
Kenya

Corresponding author:
Dr. Eugene K. Genga.
Email: eugenekalman@
gmail.com

Defining gout and hyperuricemia in sub-Saharan Africa: a review

Genga EK, Oyoo GO

Abstract

Objective: Gout is an inflammatory disease characterized by hyperuricemia. There is paucity of data on epidemiology and its overall impact in an African setting. Once thought to be rare in Africa, the numbers are increasing with more Africans adopting a western lifestyle. In view of these observations, this review looks to shed light on gout in sub-Saharan Africa.

Recent findings: Drivers of the surge in numbers of gout and hyperuricemia in Africa include the adoption of western lifestyle, higher socio-economic status, male sex and excess alcohol consumption. Further contributions are from the rising number of lifestyle diseases such as obesity, hypertension and diabetes.

Conclusion: There are increasing numbers of publications reflecting a growing recognition of gout in sub-Saharan Africa (sSA).

Key words: Gout, Hyperuricemia, sub-Saharan Africa

Introduction

Gout is an inflammatory crystal deposition disease characterized by hyperuricemia. Serum urate levels exceed 6.8mg/dl (400 micromol/l) which is the approximate limit of urate solubility. There has been a global increase in the burden of gout. Once thought to be the preserve of Western countries, there has been a paradigm shift with increasing numbers in the developing world. This can be attributed to the spread of western lifestyles to these

regions with improved case detection via better diagnostic facilities and clinical expertise¹. In Africa the overall impact of gout and hyperuricemia has been underestimated. This review looks into data from epidemiological studies in the rich diverse continent of sSA on gout and hyperuricemia. This review will try to explain the reasons for the surge in gout numbers and its impact.

Epidemiology of gout in sub-Saharan Africa

There are many challenges facing Africa including limited financial resources, misuse of finances, malnutrition, poor water and sanitation amongst others. The available health care resources are overburdened by the high burden of communicable diseases and the rising prevalence of non-communicable diseases. Rheumatic diseases are therefore not considered a high priority by the various African governments. This is compounded by the low numbers of rheumatologists working across the continent. The recommended numbers should be one per 100,000 people as per WHO standards². Thus, there is paucity of epidemiological data on rheumatic diseases, gout included. Usenbo *et al*³ reported that gout is the 3rd most common arthritis in Africa after osteoarthritis and rheumatoid arthritis. HIV has changed the landscape of gout with case reports of protease inhibitor associated gout. Ouédraogo *et al*⁴ reported gout as the third most common inflammatory arthritis after rheumatoid arthritis and HIV associated spondyloarthropathy. Gout and hyperuricemia are

Table 1: Gender and age in presentation of gout in selected studies in Africa

	Male: Female ratio	Mean age on onset in years	Sample population
Mody <i>et al</i> ¹³	3.8:1		19
Cassim <i>et al</i> ⁶	6.6:1	50.5	107
Tickly <i>et al</i> ⁹	3.3: 1		90
Bileckot <i>et al</i> ⁵	19:1	51	60
Adelewo <i>et al</i> ¹¹	2.8:1	53.4	146
Oyoo ¹⁰	9.5:1	47.5	21
Mijinyawa <i>et al</i> ⁸	15.9:1	44	160

predominantly seen in male Africans above the age of 50 years. The male to female ratio ranges from 3.3:1 to as high as 19:15-11.

Time to diagnosis is still too long. Mijinyawa¹² recorded a mean duration of 8 years before diagnosis was made. Other studies found that it took the patients about 3-4 years before the diagnosis was made¹¹⁻¹³. Reasons for this delay include poor medical resources and a low index of suspicion by clinicians.

Clinical presentation

The most common presentation recorded in most case series is mono articular. However, Bileckot *et al*⁵ and Lutalo¹⁴ had a predominant oligoarticular and polyarticular presentation but this could be attributed to the long duration before diagnosis. In the case series by Lutalo¹⁴ apart from the polyarticular presentation, they all had tophi. Lutalo¹⁴ also noted that one third of the cohort had been diagnosed late. The knee, ankle and first metatarsophalangeal joints are the most commonly afflicted⁵⁻¹⁵. There are still large numbers of patients with tophi which is worrying⁵⁻¹⁵. This can be attributed due to the late presentation and diagnosis of the disease. Gout in post-menopausal women is commonly misdiagnosed because of atypical presentation as hands and feet have small joint polyarthropathy especially in those on diuretics.

Risk factors for gout in Africa

There has been a surge in numbers of patients with gout across the sub-continent due to mainly the adoption of a Western lifestyle also associated with an increase in

cardio-metabolic diseases⁵⁻¹⁵. The majority of those afflicted reside in an urban setting and belong to the middle and higher socio-economic classes⁷. For example, Tickly *et al*⁹ observed gout to be more prevalent in patients with white collar jobs. The drivers in this study had changes in socio-economic status leading to a change in diet switch from a vegetable/cereal-based diet to meat and carbohydrate and an increase in alcohol intake. A number of studies have shown gout to be associated with diabetes, obesity, hypertension, kidney disease, dyslipidemia, excess alcohol consumption and the increased usage of drugs such as diuretics and statins in patients with cardio-metabolic disease⁵⁻¹⁵.

The impact of hyperuricemia has been underestimated in Africa. There are a few studies looking at hyperuricemias and associated illnesses. A South African study by Ranjith *et al*¹⁷ on myocardial infarct patients noted that 26% had hyperuricemia. They concluded that hyperuricemia was associated with hypertension, renal dysfunction and mortality from myocardial infarct. Mapoure *et al*¹⁸ noted in his study that one in two black patients with stroke had hyperuricemia and still remains a predictor of poor outcome. A Ghanaian study by Sarfo *et al*¹⁹ on stroke reported higher numbers (46.3%) of hyperuricemia and was associated with increased mortality. There may be a role of genetic predisposition to gout as a number of studies have noted that some of the study participants have a strong family history of gout. Mijinyawa¹² noted the 11% had a family history of gout. Ndong Atome *et al*⁷ found that those with family history of gout had an eight times increased risk to develop the disease. A South African study by Cassim *et al*⁶ went a step further and isolated a gene HLA-B14 as possible risk factor for the development of gout. There have been some

Table 2: Clinical presentation of gout in selected studies in Africa

	Monoarticular	Oligoarticular	Polyarticular	Tophi
Mijinyawa ¹²	59%	43%	11%	19%
Mody <i>et al</i> ¹³	26%		74%	47%
Malemba <i>et al</i> ¹⁵	36%	38.9%		7%
Cassim <i>et al</i> ⁶	37.4%	28%	34.6%	
Tickly <i>et al</i> ⁹	55.6%		44.4%	51.1%
Oyoo ¹⁰	47.6%	19.1%	33.3%	19.1%
Adelowo <i>et al</i> ¹¹	50%	35.6%	14.4%	6.2%

Table 3: Risk factors for gout in selected studies in Africa

	Obesity	Hypertension	Diabetes	Dyslipidemia	Alcohol	Renal insufficiency
Tickly <i>et al</i> ⁹	✓	✓			✓	
Ndong <i>et al</i> ⁷	✓	✓	✓		✓	
Mijinyawa ¹²	✓	✓			✓	
Bileckot <i>et al</i> ⁵	✓	✓	✓		✓	✓
Doualla-Bija <i>et al</i> ¹⁶	✓	✓		✓	✓	✓
Adelowo <i>et al</i> ¹¹	✓	✓	✓			✓
Oyoo ¹⁰	✓	✓	✓		✓	

interesting cases on gout and hyperuricemia that may be unique to the African continent. A review by Bileckot *et al*⁵ on 60 patients from Congo with gout had one patient with sickle cell disease. A Kenyan study by Adam²⁰ found that having hyperuricemia can be a risk factor to develop vertigo.

Conclusion

There is an emergence of gout and hyperuricemia across the African continent. The drivers are compatible to what is known around the world. The adoption of western lifestyle especially in the higher socio-economic groups has played a major contribution. Other contributions are from rising numbers of patients with obesity, hypertension, diabetes, dyslipidemia and chronic kidney disease. The majority of patients have a strong family history of the disease, are male and aged above 50 years. More effort should be put towards education on choice of medicines especially hypertension as diuretic therapy has been strongly implicated in a number of hyperuricemia cases. Africa has some unique presentations of hyperuricemia with associations with HIV, sickle cell disease and vertigo. Time to diagnosis is still too long. Efforts should be made to come up with simplified guidelines tailor made for a resource limited set-up which is the case in Africa.

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Department of Clinical
Medicine and Therapeutics,
School of Medicine,
College of Health Sciences,
University of Nairobi, P.O.
Box 19676-00202, Nairobi,
Kenya

Corresponding author:
Dr Matilda AC Wendo.
Email: matildawendo@
gmail.com

Prevalence of peripheral neuropathy and its electrophysiological types in patients with systemic lupus erythematosus at Kenyatta National Hospital

Wendo ACM, Oyoo GO, Kwasa TOO, Maritim MC, Nakitare S, Kwasa J

Abstract

Background: Peripheral neuropathy, one of the neuropsychiatric syndromes of Systemic Lupus Erythematosus (SLE), occurs in 2% to 36% of patients. It has been associated with high disease activity indices and poor quality of life scores. Studies have demonstrated benefits of early identification and treatment on the severity and progression of neuropathy. There is paucity of data on neurological manifestations of SLE in Africa.

Objective: To determine the prevalence of peripheral neuropathy using clinical evaluation and Nerve Conduction Studies (NCS) and to describe its electrophysiological types using NCS; to determine and correlate quality of life with presence of peripheral neuropathy among SLE patients attending Kenyatta National Hospital (KNH), Rheumatology Clinic.

Design: This was a cross-sectional study of SLE patients attending Rheumatology outpatient clinic at KNH.

Methods: Forty eight patients with a diagnosis of SLE as per the 2012 Systemic Lupus International Collaborating Clinics (SLICC) criteria who were 18 years and above were included in the study. Socio-demographic data and clinical information were obtained from the patients medical records. Structured history and clinical examination was performed on all patients. Lupus quality of life questionnaire was administered and nerve conduction studies performed on all patients.

Results: The overall prevalence of peripheral neuropathy was 60.4% (29 out of 48). Of these 27.1% were symptomatic for peripheral neuropathy and had abnormal nerve conduction studies while 25% were symptomatic for peripheral neuropathy and had normal nerve conduction studies. The other 8.3% had abnormal nerve conduction studies despite being asymptomatic. The most common nerve conduction pathology was demyelination 9 (52.94%, n=17). However excluding 5 patients found

to have Carpal tunnel syndrome, then demyelination was 4 (23.52%, n=17), while axonopathy was found in 5 (29.41% n=17) of the patients. The most prevalent nerve conduction syndromes was motor neuropathy (52.94%, n=17). There was a significant correlation between the presence of peripheral neuropathy with lower quality of life scores involving the domains of physical health ($p < 0.001$), pain ($p = 0.012$), planning ($p = 0.003$), and fatigue ($p = 0.005$).

Conclusion: There is a high prevalence of peripheral neuropathy among SLE patients, with variable clinical and electrophysiologic presentation. Quality of life scores are lower in affected patients.

Key words: Peripheral neuropathy, SLE, Kenya, Neuropsychiatric, Africa

Introduction

Systemic Lupus Erythematosus (SLE) is a prototypic chronic inflammatory autoimmune disease with a wide spectrum of clinical presentation affecting almost all organs and tissues, including the nervous system. Neurological manifestations, occurs in 10% - 90% of SLE patients¹⁻⁴. In Africa there is paucity of data on the prevalence of neurological disorders among SLE patients. Genga *et al*⁵ in Kenya reported a prevalence of 19% while Wadee *et al*⁶ from South Africa reported a prevalence of 15.9%. These low numbers of neurological disorders was mainly represented by patients with stroke, new onset seizures, psychosis and did not include neuropathies.

Peripheral neuropathy in SLE is one of the neuropsychiatric syndromes defined by the 1999 revised American College of Rheumatology as acute inflammatory demyelinating radiculopathy (Guillen-Barre Syndrome), autonomic disorder, mononeuropathy-single/multiplex, myasthenia gravis, cranial neuropathy, plexopathy and polyneuropathy⁷. Recent studies now show that small fiber neuropathy not described in 1999 ACR

case definitions of neuropsychiatric syndromes to be common in SLE patients while plexopathy and Guillen-Barre syndrome uncommon^{8,9}.

Peripheral neuropathy is thought to occur in 2% to 36% of patients with systemic lupus erythematosus. In Africa there is not much data on prevalence and clinical associations of peripheral neuropathy with SLE. However Gbané-Koné *et al*¹⁰ in Cote d' Voire , and Genga *et al*¹¹ in Kenya have reported cases of peripheral neuropathy. Oomatia *et al*⁸ and Brundusa *et al*¹² associated peripheral neuropathy in SLE with a high disease activity indices and poor quality of life scores.

Materials and methods

This was a hospital based cross-sectional study conducted from May 2018 to July 2018, in the Rheumatology outpatient clinic at the Kenyatta National Hospital, Nairobi. The study commenced after obtaining all the necessary ethical approvals from the institutional review board. All patients aged 18 years and above fulfilling the 2012 SLICC classification criteria for SLE diagnosis were eligible for the study. Patients were excluded if they were amputees, had history of traumatic involvement affecting the nerves, had foot ulcerations, as well as those known to have other known causes of peripheral neuropathy such as mixed connective tissues disease, diabetes mellitus, history of heavy alcohol consumption, chronic renal failure and pernicious anaemia. All participants gave an informed written consent. Consecutive sampling method was applied.

All participants had a clinical history and a targeted neurological examination done. Lupus quality of life questionnaire was administered and nerve conduction study was carried out by a qualified neurologist with experience in electrophysiological studies on all participants.

Peripheral neuropathy was defined both clinically and electrophysiologically as: presence of a symptom, and or a sign, with or without impairment in nerve conduction studies or such impairment without a sign or symptom. All the NCS were carried out at room temperature on a Nihon Cohden Machine and the Median, Ulnar, Peroneal, Tibial and Sural nerves tested.

Data was coded, entered and managed in a Microsoft Access 2013 database. Statistical analysis was done using Statistical Package for Social Sciences version (SPSS) 25.0. Data was summarized into proportions for categorical variables, and into means (SD) or medians for the continuous variables. Prevalence of peripheral neuropathy was analyzed and presented as proportions with 95% confidence interval. Chi-square test was used to check for association between patient profile with the presence of peripheral neuropathy. A p value of less than or equal to 0.005 was considered statistically significant.

Lupus quality of life was scored and analyzed using a standard scoring system resulting in scores between 0 to 100. Health related quality of life was correlated with peripheral neuropathy using chi-square analysis.

Results

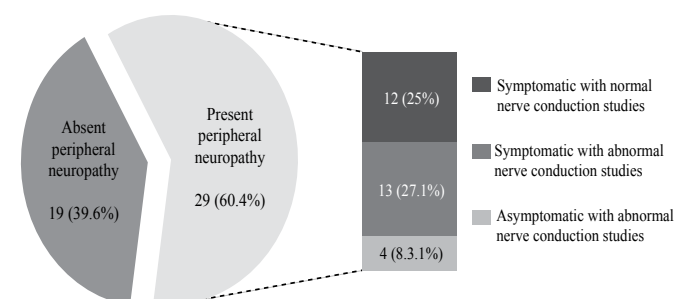
In a period of 3 months (May 2018 to July 2018), 48 patients with SLE were recruited into the study. The entire study population comprised of females whose mean age was 37.9 years (SD 11.92, SEM 1.72). The median duration of disease since diagnosis was 27.5 months (IQR 12.0-60.0). The most commonly used disease modifying agents was hydroxychloroquine at 97.9%, with a mean duration of usage of 38.46 months as outlined in Table 1.

Table 1: Medications taken by study participants (n=48)

Medication	Yes (%)	Mean duration of treatment (months)	SD
NSAIDs	17.1	27.27	32.98
HCQ	97.9	38.46	38.59
Leflunomide	4.2	43.5	40.31
MTX	14.6	24.86	31.46
Cyclosporine	0	0	0
MMF	25.0	24.19	15.90
AZA	37.5	35.24	46.85
Steroids	85.4	41.9	42.21
Biologics	0	0	0

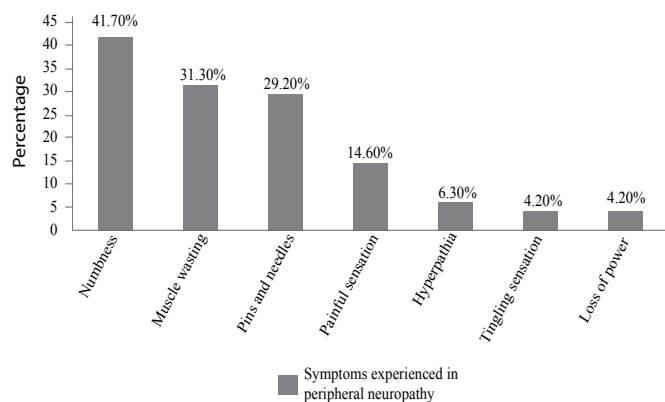
The overall prevalence of peripheral neuropathy in this population was 60.4%. Of these 27.1% were symptomatic with abnormal nerve conduction studies, while 25% were symptomatic with normal nerve conduction studies. Eight point three per cent were found to be asymptomatic with abnormal nerve conduction studies, as shown in Figure 1.

Figure 1: Prevalence of peripheral neuropathy and its presentation in the study participants (sample population n=48)



The frequencies of various neurological symptoms experienced at the time of presentation are shown in Figure 2. The most common symptoms complaint was numbness at 41.7%. Some patients had more than one complaint in terms of the symptoms.

Figure 2: Symptoms experienced in peripheral neuropathy in the study population



Demyelination was the most common nerve conduction pathology detected among participants in this study with a prevalence of 9 (52.9%) out of 17 participants with abnormal nerve conduction studies. However, excluding 5 patients found to have Carpal tunnel syndrome, then the prevalence of demyelination was found to be lower with 4 (23.5%) study participants affected. Axonopathy was found in 5 (29.4%) of the study participants (n=17) (Table 2). Motor neuropathy was found to be the most common type of nerve conduction syndrome with 9 (52.9%) of the study participants affected

(n=17) as shown in Table 2. No patient had mononeuritis multiplex as outlined in Table 2. Carpal tunnel syndrome was found in 5(29.4%) of the study participants (n=17).

The overall score for health related quality of life as determined by the LUPUS QOL questionnaire in our study participants was generally impaired quality of life in all the six domains. The domain with the lowest score was physical health (59.1). The summary of the findings are outlined in Table 3.

Table 3: Lupus QOL score of study population (n=48)

Transformed domain	Median (IQR)
Physical health	59.1 (53.1)
Emotional health	75.0 (33.3)
Pain	75.0 (29.3)
Planning	75.0 (58.3)
Fatigue	68.8 (37.5)
Burden to others	75.0 (23.3)

From the sample population, the correlations between presence of peripheral neuropathy and lower quality of life scores in the domains of Physical health, pain, planning and burdens to others were statistically significant as depicted on Table 4.

Table 2: Electrophysiological types of peripheral neuropathy in the study participants

Electrophysiological types	Variables	Frequency n=17	(%)
Nerve conduction pathologies	Demyelination	9	52.9
	Axonopathy	5	29.4
	Axonopathy & demyelinating	3	17.7
Nerve conduction syndromes	Motor	9	52.9
	Sensory- motor	5	29.4
	Sensory	3	17.37
	Mononeuropathy	8	47.1
	Mono-neuritis multiplex	-	-
	Carpal tunnel syndrome	5	29.4

Table 4: Association of peripheral neuropathy with quality of life of patients in the study

Variable	Peripheral neuropathy		X ²	Odds ratio	P value
	Yes n=29 (%)	No n=19 (%)			
Physical health (<80)	21 (72.4%)	4 (21.1%)	12.13	9.84	<0.001
Emotional health (<80)	19 (65.5%)	9 (47.4%)	1.66	2.11	0.212
Pain (<80)	15 (51.7%)	3 (15.8%)	6.32	5.71	0.012
Planning (<80)	17 (58.6%)	3 (15.8%)	8.66	7.56	0.003
Fatigue (<80)	20 (69.0%)	11 (57.9%)	0.62	1.62	0.433
Burden to others (<80)	19 (65.5%)	11 (57.9%)	8.01	11.10	0.005

*X²- Chi Square results (Pearson's) on R software

*Significant associations are underlined in the table

Discussion

The overall prevalence of peripheral neuropathy in this population of SLE patients was found to be high at 60.4%. The prevalence of peripheral neuropathy in SLE in our study was higher than those that had been done worldwide in Europe and in Asia. This study defined peripheral neuropathy both clinically and electrophysiologically therefore yielding a high prevalence of peripheral neuropathy unlike the other studies that defined peripheral neuropathy either clinically only or electrophysiologically only.

Saigal *et al*¹³ in North Asia found a prevalence of 36% (18 out of 50), after having defined peripheral neuropathy electrophysiologically, however they did not include those patients who were symptomatic for peripheral neuropathy and were found to have normal nerve conduction study. Khean *et al*¹⁴ in South Asia found a high prevalence of 56% (28 out of 50) of patients with SLE to have abnormal nerve conduction studies; this high prevalence could have been attributed to external nerve compression in bed ridden patients as the study populations mainly comprised of in-patients, unlike our study that looked at ambulatory out-patients attending rheumatology out patient clinic. Brundusa *et al*¹² found a prevalence of 14%. This low prevalence was mainly because peripheral neuropathy was defined clinically as per the ACR nomenclature and case definition of neuropsychiatric manifestation of SLE.

The high prevalence of peripheral neuropathy in our study could also be explained by the late presentation of SLE patients in our set up and also our patients could have had a high disease activity index, which studies have found to correlate with the presence of peripheral neuropathy, though our study did not assess for disease activity index. Racial difference with genetic variability may also explain the wide discrepancy on the prevalence of peripheral neuropathy as most studies on prevalence of peripheral neuropathy were conducted in Europe, Asia and America. There was paucity of similar studies done in Africa.

Twelve (25%) patients with symptomatic peripheral neuropathy in our study were found to have normal nerve conduction studies; this probably represent patients who may have involvement of small diameter nerve fiber that is not picked on nerve conduction studies and these patients would benefit from either skin or nerve biopsy for confirmatory diagnosis. These results were comparable to other studies done by Oomatia *et al*⁸ who found that 17.1% (14 out of 82) of SLE patients with peripheral neuropathy had small fiber neuropathy while Gøransson *et al*⁹ found 13%. These studies performed punch skin biopsy to confirm the diagnosis however in our study skin and nerve biopsy were not performed. Oomatia *et al*⁸ found that small fiber neuropathy was commonly observed in SLE patients than mononeuritis multiplex, plexopathies, and demyelinating neuropathies. Non length dependent small fiber neuropathy associated with skin biopsy result

suggestive of dorsal root ganglion neuronal cell loss was reported by Oomatia *et al*⁸. Therefore small fiber neuropathies not included in the ACR neuropsychiatric case definitions of peripheral neuropathies SLE is rather a common finding.

Thirteen (27.1%) patients with symptomatic peripheral neuropathy, had abnormal nerve conduction studies. This was similar to a study by Saigal *et al*¹³ in North Asia where they found that 9 out of 18 patients with SLE were symptomatic for peripheral neuropathy and had nerve conduction study abnormality hence clinical peripheral neuropathy.

The remaining 4 (8.3%) patients in our study were asymptomatic and had abnormal nerve conduction studies, and represented a group of patients with sub-clinical peripheral neuropathy. This was almost similar to Saigal *et al*¹³ who found that 9 out of 18 patients with peripheral neuropathy had sub-clinical peripheral neuropathy.

In our study, demyelination was found to be the most common type of nerve conduction pathology with 9 (59.9%) patients affected. In contrast to other studies done that found axonopathy to be the most common type of peripheral neuropathy¹²⁻¹⁴. However, on excluding 5 patients with Carpal tunnel syndrome, then the prevalence of demyelination was found to be lower at 4(8.33%) in this study, therefore comparable findings to the other studies that did not include Carpal tunnel syndrome. Five (29.4%) patients had axonopathy hence suggestive of vasculitic neuropathy as expected to occur in patients with SLE and this was consistent with what was found in previous studies¹³.

Most of our patients had 9 (52.9%) had motor neuropathy as the most common type of peripheral neuropathy. This was similar to a study done by Saigal *et al*¹³ who found that electrophysiological motor nerve parameters were frequently abnormal compared to sensory parameters.

Five (29.4%) patients had Carpal tunnel syndrome, which is mononeuropathy of the median nerve, representing patients who could have had active SLE disease with inflammation of wrist joint.

This study found that presence of peripheral neuropathy could have led to poor quality of life as concerns the domains in physical health, pain, planning and burdens to others. These findings were similar to a study by Brundusa *et al*¹² who found that patients with peripheral neuropathy had significantly lower SF 36 score especially in the physical components, hence poor quality of life.

Conclusion

This study demonstrates a high prevalence of peripheral neuropathy among SLE patients. Small fiber neuropathy which presents with symptoms and normal nerve conduction studies may be rather a common finding in SLE patients in our population. The proportion of patients with demyelination were substantially high

however excluding patients with Carpal tunnel syndrome then axonopathy was rather a common finding. Motor neuropathy was more prevalent. There was a correlation between presence of peripheral neuropathy with quality of life as concerns domains in physical health, pain, planning and burdens to others.

Study limitation

We were unable to exclude all confounding causes of peripheral neuropathy in our population due to resource limitation. Sural nerve biopsy and skin punch biopsy were not performed to further characterize the neuropathies in instances where nerve conduction study was non-revealing, due to financial constraints. Electromyogram was not conducted in our study due to time and resource limitation. This was a hospital based study therefore not generalizable.

Recommendations

A prospective study to determine the progression and outcome of peripheral neuropathy seen in SLE patients in our setting. Skin and nerve biopsy to be included in future studies especially in instances where nerve conduction studies were none revealing. Electromyogram to be incorporated in subsequent studies for confirmatory diagnosis of radiculopathy. Base line symptom screen for peripheral neuropathy in all SLE patients.

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Department of Clinical
Medicine and Therapeutics,
School of Medicine,
College of Health Sciences,
University of Nairobi, P.O.
Box 19676-00202, Nairobi,
Kenya

Corresponding author:
Dr Bernard O Odundo.
Email: odundob@gmail.com

Prevalence of functional disability in patients with rheumatoid arthritis attending the rheumatoid outpatient clinic at Kenyatta National Hospital

Odundo BO, Ogola EN, Oyoo GO, Genga EK

Abstract

Background: Rheumatoid Arthritis (RA) causes serious joint erosion, deformity and severe functional disability if not diagnosed early and followed by a timely initiation of Disease Modifying Anti-Rheumatic Drugs (DMARDs). Studies have shown that functional disability is a major determinant on the patients' quality of life and it is a strong predictor of morbidity, work disability and mortality. Functional disability is measured by patient-oriented tools such as the Health Questionnaire Disability Index (HAQ-DI) which is the gold standard tool.

Objective: This study aimed to determine the prevalence of RA functional disability and its association with disease activity, socio-demographic and clinical characteristics in patients with rheumatoid arthritis on follow up at the Rheumatology Outpatient Clinic in Kenyatta National Hospital (KNH).

Design: This was a descriptive cross-sectional hospital-based study.

Setting: Rheumatology Outpatient Clinic (ROPC) at the Kenyatta National Hospital (KNH); the largest public national and referral hospital in Kenya.

Subjects: One hundred and six patients who fulfilled the 2010 American College of Rheumatology and the European League Against Rheumatism (ACR-EULAR) criteria.

Results: There were 102(96.2%) females and 4(3.8%) males recruited into the study with a female to male ratio of 10:1. The prevalence of functional disability was 72.6% with a mean HAQ-DI of 0.41 ± 0.38 which is interpreted as mild disability. Active disease was present in 90.6% of the patients with a median CDAI of 11 (IQ range 6.5-22) and mean CDAI score of 15.95 ± 13.08 which represents moderate disease activity and only 9.4% were in remission. The average duration of disease was 5.1 years. Functional disability was significantly correlated with disease duration and treatment duration.

Conclusion: The study demonstrated a high prevalence of functional disability

and a higher disease activity of among RA patients in our setting despite being on DMARDs. There was a significant correlation between functional disability and disease duration. However, there were no correlations between functional disability and any of the socio-demographic study variables; age, sex, marital status, employment, education and smoking history.

Introduction

Rheumatoid Arthritis (RA) is a chronic systemic autoimmune and the most common inflammatory arthritis that often leads to varying degrees of functional disability. It has been estimated that more than half of all patients with RA will deteriorate to severe functional disability after 10 years of the disease¹. Functional disability is a strong independent predictor other long term outcomes such as work disability, morbidity and mortality^{2,3}.

We used the Health Assessment Questionnaire-Disability Index (HAQ-DI) to assess. HAQ-DI the patient's ability to perform Activities of Daily Living (ADL) such as dressing, eating, toileting, shopping, and travelling. The disease activity was assessed using the Clinical Disease Activity Index (CDAI) which excludes laboratory parameters.

Materials and methods

This was a hospital-based cross-sectional descriptive study conducted between 2nd August and 11th October 2018 targeting RA patients attending KNH Rheumatology Outpatient Clinic. The study was approved by the institutional ethics and research review board. Patients with a file diagnosis of RA at the ROPC were screened consecutively until a sample of 106 was reached. All patients recruited fulfilled the inclusion criteria: aged 18 years and above who met the 2010 American College of Rheumatology-European League Against Rheumatism (ACR-EULAR) criteria for RA⁴ and gave written informed consent.

Targeted clinical history for socio-demographic such as age, sex, employment and marital status and for clinical variables such as disease duration and treatment modality using a data abstraction tool. Patients were then issued the HAQ-DI questionnaire for evaluation of functional status followed by joint assessment out of a 28-joint count. The patient global assessment of general health and the provider assessment of general health, both on a scale of 0-10 cm, was carried out. The composite of tender and swollen joint counts and the global assessment of general health was used to compute the CDAI score for each patient. Disease activity was categorized as remission, mild, moderate or severe disease while functional disability was categorized as no disability, mild disability, moderate to moderately severe and severe disability.

Data analysis and statistical method: Data was cleaned, verified and coded, entered into Microsoft excel database and subsequently exported to Statistical Package for Social Sciences (SPSS) 21.1. for statistical analysis. Data was summarized into proportions for categorical variables and into means (SD) or medians for the continuous variables. Continuous variables such as age and duration of disease were expressed as means and Standard Deviations (SD) and plotted in histograms. Prevalence was determined and expressed as a percentage with 95% confidence interval. For categorical variables such as sex and marital status, pie charts were plot; frequencies and proportions were reported. Correlations between functional disability to continuous variables or a categorical variable was analyzed by Pearson correlation coefficient and student t-test respectively. A significant association was a p-value of <0.05.

Results

There was a female preponderance of 102(96.2%) with a female to male ratio of 10:1. The patients were aged between 18 and 83 years and were normally distributed with a mean age of 48.4 ± 14.9 years. Fifty nine (55.6%) of the patients were employed and majority had some formal education; secondary 45(42.5%) or primary 31 (29.2%) and tertiary 21(19.8%).

Over three-quarters (88.4%) were married and majority never smoked (99.1%). Table 1 shows their socio-demographic characteristics.

Majority of the patients, 96(90.6%) had disease duration of more than a year and 67(63.2%) had treatment duration between 1-5 years. Most patients were on combination DMARD therapy, and the combination of methotrexate and hydroxychloroquine (34.9%) being the most common. None of the patients reported recent or current steroid use and none of them was on a biologic DMARD agent. However, 58(54.8%) of them reported frequent use of over-the-counter NSAIDs or intermittent short-term prescription NSAIDs. Table 2 summarizes the baseline clinical characteristics.

Table 1: Baseline socio-demographic characteristics of the participants

	Socio-demographic variables	Frequency (n)	(%)
Age (years)	18-27	8	7.5
	28-37	22	20.8
	38-47	23	21.7
	48-57	22	20.8
	58-67	20	18.9
	68-77	7	6.6
	78-87	4	3.8
Sex	Male	4	3.8
	Female	102	96.2
Marital status	Married	94	88.7
	Single	7	7.0
	Widowed	2	1.9
	Separated	3	2.8
Employment status	Unemployed	47	44.3
	Employed	19	17.9
	Self employed	40	37.7
Education level	None	9	8.5
	Primary	31	29.2
	Secondary	45	42.5
	Tertiary	21	19.8
Smoking history	No	105	99.1
	Yes	1	0.9

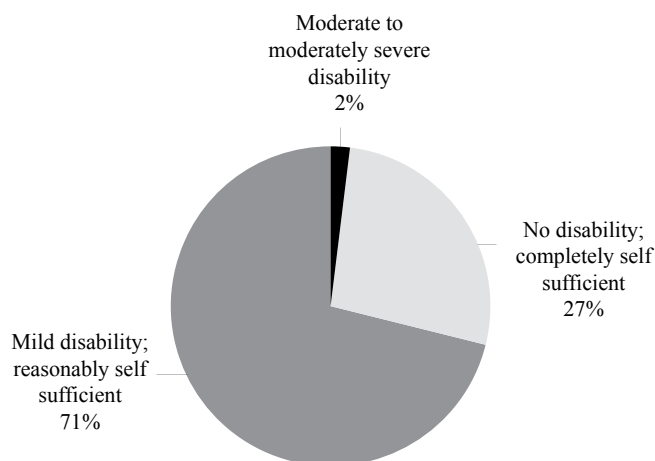
Table 2: Baseline clinical history of study participants

Clinical history	Frequency (n)	(%)
Treatment duration		
<1	8	7.5
1-5	67	63.2
>5	31	29.2
Treatment modality		
DMARDs		
HCQ	16	15.1
LEF	11	10.4
LEF/HCQ	19	17.9
LEF/SSZ	3	2.8
MTX	10	9.4
MTX/HCQ	37	34.9
MTX/LEF	10	9.4
NSAIDs	58	54.8
GC	0	0
Biologic	0	0
Disease duration		
<1	8	7.5
1	2	1.9
>1	96	90.6

*HCQ -Hydroxychloroquine; LEF-Leflunomide; SSZ -Sulfasalazine; MTX -Methotrexate; NSAIDs -Non-steroidal anti-inflammatory drugs; GC-Glucocorticoid

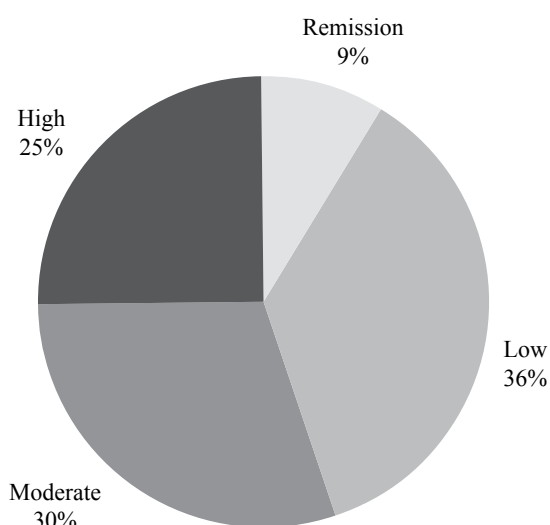
Prevalence of functional disability: Of the 106 patients evaluated, 77(72.6%) were found to have functional disability out of which the majority 75(70.8%) had a mild disability and only 2(1.9%) had moderate to moderately severe disability with HAQ-DI scores of $>1.25 \leq 2.00$. The mean HAQ-DI score was $0.41(\pm 0.38)$ and a median HAQ-DI of $0.5(0.00-0.625)$ which translated to majority having mild functional disability (Figure 1).

Figure 1: Prevalence of functional disability



Prevalence of active disease: Ninety six (90.6%) of the patients had an active disease and only 10(9.4%) were in remission (Figure 2). Of those with active disease, 38(35.8%) had low disease activity, 32 (30.2%) had moderate disease activity and 26(24.5%) had high disease activity. The mean CDAI score was $15.94(\pm 13.08)$ interpreted as moderate disease activity, median of CDAI was 11(6.5-22).

Figure 2: Disease activity



Association of HAQ-DI to socio-demographic characteristics: None of the socio-demographic variables was found to be significantly correlated with HAQ-DI ($P > 0.05$).

Association of HAQ-DI to disease specific variables: HAQ-DI was found to be significantly correlated with treatment duration ($p=0.037$) and disease duration ($p=0.047$). The use of DMARDs was also found to be correlated to HAQ-DI. However, disease activity (CDAI) was found not statistically correlated to HAQ-DI ($p=0.63$).

Discussion

The study found an overall prevalence of functional disability in this population of RA patients to be 72.6% with a mean $\pm$ SD HAQ-DI score of 0.41 ± 0.38 , median HAQ-DI of 0.5 (IQR: $0-0.63$). Only 17.4% had no disability. Though the prevalence was high in our study, majority of the patients (71%) had mild disability and were reasonably self-sufficient. Only 2% had moderate to moderately severe disability. This prevalence is comparable but lower to that found in similar studies in Africa. In South Africa, in a study of functional disability in 108 RA patients at a public healthcare clinic, Westaway *et al*⁵ found an overall prevalence of 83%; the median HAQ-DI score was 1.6 translated as moderate to moderately severe disability, though majority (61%) of the patients in their study had worse HAQ-DI scores of >1.2 . Basma *et al*⁶ in Libya, in a study of HRQOL of 100 RA patients, found a median HAQ-DI score of 0.75 and 63% of patients had HAQ-DI of between 0-1. However, in this study by Basma *et al*⁶ they had a selection bias; they recruited only pre-selected patients with DAS28 scores of 2.6-5.1 and excluded patients in remission and those with high disease activity. In China, Zhao *et al*⁷ in a cross-sectional study, the incidence and influencing factors of functional disability in Chinese patients with RA, found a lower prevalence of 58.5% with mean $\pm$ SD HAQ-DI scores of 0.665 ± 0.675 and patients with better pain management with a good social support showing better physical function scores.

Most of the patients in our study had an active disease and only 10(9.4%) were in remission despite all of them being on therapy with DMARDs. Therefore, this could warrant the need for tighter control of disease activity. It is rather not surprising that over half (54.8%) of our patients were on intermittent NSAIDs and majority were on combination DMARDs. A high number of patients on combination DMARDs had longer treatment duration between one to five years.

Although, steroids are indicated in early aggressive disease and to alleviate symptoms in acute flares, none of our study subjects was on steroids may be due to adherence to current treatment guidelines that recommends steroid sparing and emphasizes the early use of synthetic DMARDs to achieve remission in a treat-to-target strategy⁸. Ndirangu *et al*⁹ in a Master of Medicine thesis in a study of disease activity measures in RA in this same population found 62.5% of the patients were on steroids. A similar trend by Basma *et al*⁶ also showed 65% of the patients in the study were on steroids.

None of the patients in our study was on biologic agents which have been shown to improve outcome in patients with suboptimal response and/or intolerance to traditional DMARDs, probably due to the prohibitive cost of biologics and considering that our setting is a public health facility where most of our patients may not afford to sustain biologic therapy. Oyoo *et al*¹⁰, in a study of rituximab, a monoclonal antibody to B-cells, in RA patients with suboptimal response to traditional DMARDs in RA who had to be switched to rituximab found a significant improvement in disease activity, functional and disability indices after six months of therapy.

Although this study found a statistically significant correlation of functional disability (HAQ-DI) to disease duration ($p=0.047$) and treatment duration ($p=0.037$) it was not powered enough to assess the association of treatment modality to functional disability. However, this finding may point to a progressive disease with structural joint damage that can only be assessed radiographically which was a limitation in this study due to resource constraint¹¹. This association was in keeping with similar studies that assessed the correlation of disease duration to functional disability. In a longitudinal study of response to therapy of 134 DMARD-naïve patients in South Africa, Hodgkinson *et al*¹² found significant improvement in functional disability and HRQOL as assessed by HAQ-DI and SF-36 after 12 months of traditional DMARD therapy but substantial functional disability (HAQ>5) persisted in 69% of the patients.

There was no significant correlation of functional disability to any of the socio-demographic variables. This finding was similar to the study by Oyoo *et al*¹⁰ in similar population in Kenya where no association was found between functional disability using SDAI and different variables such as age, type of DMARD and steroid used though the study was not powered enough to make significant conclusions out of these findings. However, Solomon *et al*¹³, in a comparative study of functional disability in patients with RA in public health care and private health care in South Africa, found worse physical function in the former signifying poor disease management due to socioeconomic factors. This was a single center study in a public health care facility hence probably there were no overall significant socio-economic differences that would impact on functional capacity. In a systematic review of the impact of educational level on RA, Lopez-Castillo *et al*¹⁴ found that educational level influenced the risk and clinical course of RA and low educational level worsened functional disability and work disability. This study found most patients (63.3%) had a high formal education and majority had good social support; 96.2% were married and 55.6% were in active employment. Though smoking has been shown to aggravate RA outcomes, only one patient was a smoker and this could not alter the overall associations of disease activity to functional disability.

Conclusion

The study demonstrated a high prevalence of functional disability and a higher disease activity of among RA patients in our setting despite being on DMARDs. There was a significant correlation between functional disability and disease duration. However, there were no correlations between functional disability and any of the socio-demographic study variables; age, sex, marital status, employment, education and smoking history. Therefore, there is need for early initiation and optimization of DMARDs together with strict monitoring of functional disability and disease activity according to guidelines to improve patient and disease outcomes in RA.

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Department of Clinical
Medicine and Therapeutics,
School of Medicine,
College of Health Sciences,
University of Nairobi, P. O.
Box 19676-00202, Nairobi,
Kenya

Corresponding author:
Dr Eugene K. Genga.
Email: eugenekalman@
gmail.com

Describing inflammatory muscle disease in Kenya: A single tertiary centre experience in Kenya

Genga EK, Atieno S, Omondi EA, Oyoo GO

Abstract

Background: Inflammatory muscle diseases are a rare group of connective tissue diseases. There is a paucity of documented literature on indigenous Africans in sub-Saharan Africa. We present herein the clinical patterns of inflammatory muscle diseases encountered at a rheumatology clinic, Nairobi, Kenya.

Objective: To describe the clinical spectrum of inflammatory myopathies at a tertiary rheumatology clinic in Nairobi. These included clinical, haematological and immunological characteristics of patients with Inflammatory myopathies.

Methods: Medical records of 10,998 patients presenting to the Nairobi Arthritis Clinic for various rheumatological conditions were reviewed. The records of 46 patients with muscle weakness with or without skin rash were selected and reviewed between January 2012 and December 2017 were retrospectively reviewed and reclassified as polymyositis (PM) and dermatomyositis (DM) based on the Bohan and Peter diagnostic criteria.

Results: Forty-six patients (F=36, M=9) were diagnosed with polymyositis and dermatomyositis. Twenty-five had possible dermatomyositis, eighteen had possible polymyositis with another three who had an overlap of polymyositis with other diseases. There were 3 patients with juvenile dermatomyositis. Majority of the patients were referred of which 14 had an alternative diagnosis to myositis. The mean age for PM was 36.36 years and for DM 41.13 years. The creatinine kinase mean was 2845.4 (697-7063)u/l. Serology for ANA tested positive in 8 patients (PM=4, DM=4). The most common symptoms of DM patients included Gottron papules (12), heliotropes rash (15) and shawl sign (5). Myositis antibody screening was not performed in any of the patients.

Conclusion: Inflammatory myopathies are still rare in Kenya. The clinical spectrum is largely similar to what is known in written literature. From referral notes and diagnosis of the primary physician, there is a paucity of information about these diseases. None of the patients

had myositis antibody panel due to either unavailability or high cost of doing the tests. More effort should be on increasing awareness of diagnosis and management of these diseases.

Key words: Inflammatory muscle disease, Polymyositis, Dermatomyositis, Nairobi, Kenya

Introduction

Inflammatory myopathy is a larger term used to describe muscle diseases that represent dermatomyositis (DM) and polymyositis (PM). These group of diseases share features of muscle inflammation and proximal muscle weakness. The differentiating feature is that DM has characteristic skin manifestations¹. The clinical and serological profile of DM and PM may vary from populations through the immune pathology within the muscle tissue is constant and distinct². There are a wide variety of diagnostic criteria used with criteria of Bohan and Peter the most commonly used^{3,4}. These criteria have a number of limitations with its inability to distinguish other forms of myopathy thus can misclassify IBM patients as PM. These limitations together with recent advances such as myositis-specific autoantibodies, that are associated with distinct clinical phenotypes has led to the development of new criteria for the diagnosis and treatment of myopathies by the EULAR/ACR groups⁵. As the disease is thought to be rare in Kenya and Africa, it is poorly understood as compared to other connective tissue diseases thus diagnosis can be a challenge. This is compounded by the limited number of rheumatologists and the high costs involved in making the diagnosis and treatment. This leads to incorrect diagnosis and delays in starting the proper treatment resulting in increased morbidity and mortality. There are few reports on inflammatory myopathies in sub-Saharan Africa. In this study, we describe the spectrum of inflammatory myopathies based on Bohan and Peter's criteria 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 center. 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 10,998 patients attending the Nairobi Arthritis Clinic and those with a diagnosis of Inflammatory Myopathy (IM) based on Bohan and Peter's criteria attending the Nairobi Arthritis Clinic between January 2012 and December 2017 and had been on follow up for at least 6 months were recruited into the study. Clinical, haematological, immunological and other relevant findings from the history were obtained from the available records. Patients were classified into two as either polymyositis or dermatomyositis. Patients with conditions that may mimic IM such as endocrine disorders, adverse effects of medication, metabolic myopathies and muscular dystrophies were excluded from the study.

Data were collected from medical records using a questionnaire including demographic data, the subtype of the myopathy, referring diagnosis, gender, age at diagnosis, association with malignancy or connective tissue diseases, clinical features recorded at the time of the diagnosis and during follow up, and other systemic involvement and the pharmacological agent used. Laboratory tests comprised biochemical tests creatine phosphokinase levels (reference levels of 22 to 198 U/L), positivity of Anti-Nuclear Antibodies (ANA) and myositis antibody panel at diagnosis were documented. For each patient, the electromyography (EMG) and muscle biopsy results were recorded at the time diagnosis was made. Using Bohan's and Peter criteria for muscle biopsy, they were recorded as positive if the results had evidence of necrosis of myofibers, phagocytosis, regeneration with basophils, large vesicular sarcolemmal nuclei, and prominent nucleoli, atrophy in a perifascicular distribution, variation in fiber size and an inflammatory exudate, often perivascular was recorded as positive as per Bohan's and Peter criteria. Review of anti-rheumatic pharmacologic treatments used during the

study period included corticosteroids (intra-articular/systemic), methotrexate (MTX), azathioprine (AZA), mycophenolate (MMF) and biologic agents was done.

Results

A total of 46/10,998 patients were identified, 21 patients had PM, 21 had DM, 4 had JDM and 4 had associated diseases (systemic lupus erythematosus, HIV and mixed connective tissue disease). There were 37 females and 9 males giving a female to male ratio of 4.1:1. The ages ranged from 3 to 60 years with a mean age of 37.45 years as shown in Table 1. There were three cases of juvenile dermatomyositis. The male to female ratio was 1:2. The most common clinical presentation was proximal myopathy (100%) of patients followed by arthritis (78.2%), dysphagia (65.2%), Gottron's papules (26.1%), heliotrope's sign (21.7%) and V-shawl sign (10.8%). Two patients had interstitial lung disease. One of the patients had a malignancy as shown in Figure 1. She was 42 years diagnosed with DM who on further evaluation was found to have ductal cell carcinoma. There were two patients with HIV with polymyositis. One was a 32-year-old male on zidovudine/lamivudine/efavirenz combination and the second a 48-year-old female on atazanavir/ritonavir/ raltegravir combination. A total of 24 out of 34 patients were referred by clinicians with alternative rheumatological diagnoses other than myositis. The referrals included rheumatoid arthritis (11), connective tissue disease (5), fibromyalgia (4), scleroderma (2) cervical spondylosis (2) and myositis (10). The EMG findings were consistent with PM in 5 patients and 4 were positive for DM. The muscle biopsy results were consistent with inflammatory myopathies in 6 patients. Important to note is that EMG and muscle biopsy was not done on all patients. Myositis antibody panel was not done on any of the patients in this series mainly due to financial constraints and some had been referred already on steroid therapy.

All the patients received steroids with normalization of CK in 43.47% and muscle power in 78.7%. Other treatments included mycophenolate mofetil 11(23.9%) patients, methotrexate and hydroxychloroquine combination 8 (17.34%) patients, two patients on

Table 1: Demographic data of inflammatory myopathy from select studies in Africa

	Genga EK	Adelowo OO	Diallo M	Toumi S	Khelifa E	Mebazaa A
PM	21	7	6	20	0	0
DM	25	7	15	50	13	130
M: F	1:4.11	1:13	0:0.6	1:2.5		3:3
Mean age (years)	37.45	35		40.7	32.85	49.5
Mean CPK(u/l)	2845.4	1134				
Malignancy	1		3	12.8	2	20

azathioprine (4.3%) and one patient on rituximab (2.1%). There were 9 patients lost to follow up during this period.

Figure 1: Symptoms of patients with DM

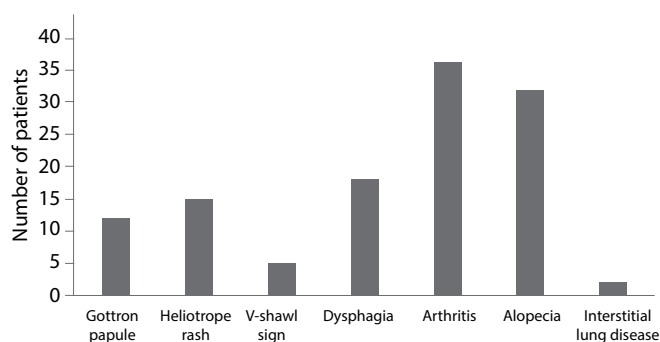
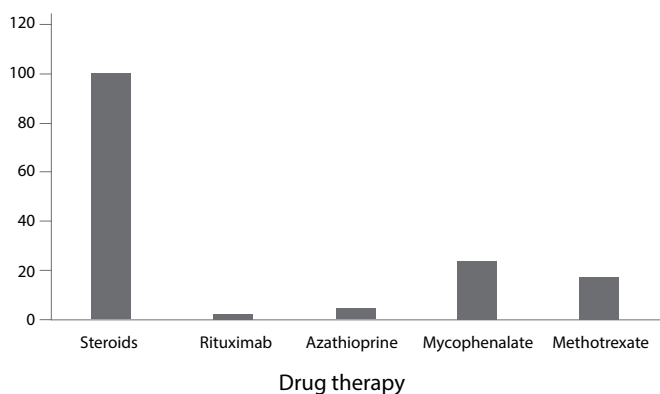


Figure 2: Steroid-sparing drugs used



Discussion

The study covered a period of 7 years and yielded 46 cases of inflammatory myopathies. This is the largest case series of inflammatory myopathies in East and Central Africa reporting on clinical and laboratory features as well as any association with malignancy and treatment modalities. This study was predominantly female with a male to female ratio of 1:4.1 with a mean age of diagnosis of 37.45 years (range from 3-60 years). This is similar to studies around the continent from Nigeria to Tunisia⁶⁻⁹. The mean age of onset is similar to other studies across the African continent⁶⁻⁹. There is a Tunisian study that differs with the above as the gender is equally balanced and had an older age of onset¹⁰. However, this looked exclusively at malignancy and dermatomyositis and may explain the difference. Our analysis shows a predominance of dermatomyositis which is in contrast to what is known in American and European literature¹¹⁻¹⁴. There were low numbers of JDM but the data largely mirrored a South African study by Faller *et al*¹⁵. Generally, our results as compared to previously reported studies show clinical feature similarities. The most common clinical presentation was proximal myopathy (100%) of patients followed by arthritis (78.2%). This is common to what is known in literature both from Africa and around the world^{8,16-18}. Involvement of other organs with myopathy is well known. The number of patients with extra-skeletal manifestations was low, take for example two in this case series had interstitial lung disease. This highlights the challenges of managing these rheumatic diseases in a poor resource set up where funds to do a comprehensive

approach to these patients is limited. This is highlighted by the low numbers of muscle biopsies, EMG and myositis antibody tests. More effort should be done by the Government and the private sector to make these tests readily accessible by improving healthcare infrastructure and lowering costs to do these tests.

There has been an association established between inflammatory myopathies and malignancy^{8,17}. A Tunisian study reported up to 90% of their cohort had myositis as a paraneoplastic symptom⁸. The most common malignancies in this cohort were breast cancer (35%) followed by nasopharynx (25%). They also reported having malignancy with a poor prognostic marker in dermatomyositis. The results of this study differ with what is known in literature where the order of malignancies is ovarian cancer, lung cancer, and pancreatic cancer^{19,20}. Asian studies report a predominance of nasopharyngeal malignancies²⁰. Our data had one malignancy. She was 42 years diagnosed with DM who on further evaluation was found to have ductal cell carcinoma. Studies have reported the association between HIV/AIDS and myopathic disease with some reporting prevalence as high as 25% of infections²². Asymptomatic elevations in CK, myalgias, and rhabdomyolysis are all possible complications of HIV. Contribution from drugs used to treat HIV for example zidovudine has been established. Studies have estimated zidovudine-induced myopathy between 8-17%²². Our study had two cases with HIV with one of the patients on the zidovudine-based regiment. A large number of our patients responded to corticosteroids which is in keeping with what is known in the literature¹⁸.

Limitations and recommendations

Our study was limited by the small sample size and its retrospective design. This may have been due to the low numbers of inflammatory muscle disease generally. Due to financial constraints most patients were unable to do muscle biopsies and myositis antibodies. This may have made us miss out on further subclassifying our patients. A recommendation would be for longer follow up looking into prognostic and survival of these patients. As per the referral diagnosis sent by our colleagues, another recommendation would be to improve knowledge of myositis in Kenya and also making diagnostic tests more readily available and affordable. This will help improve the holistic approach including diagnosis, malignancy screening, and management of these patients.

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Department of Clinical
Medicine and Therapeutics,
School of Medicine,
College of Health Sciences,
University of Nairobi,
P. O. Box 19676-00202,
Nairobi, Kenya

Corresponding author:
Dr M Shokat.
Email: mufaddal00@
hotmail.com

Burden of hyperuricemia among ambulatory patients with Type 2 diabetes at Kenyatta National Hospital diabetes outpatient clinic

Shokat M, Oyoo GO, Kamau E, Genga EK

Abstract

Background: The prevalence of hyperuricemia has been increasing around the world accompanied by a rapid increase in obesity and diabetes. Hyperuricemia has been positively associated with hyperglycemia. This study was carried out to determine the prevalence especially in Kenya where there is limited data on prevalence of hyperuricemia in diabetes.

Objective: To determine the prevalence of hyperuricemia among ambulatory patients with Type 2 diabetes at Kenyatta National Hospital.

Methods: This was a descriptive cross-sectional study. Simple random sampling was employed to recruit eligible participants. Height, weight and blood pressure was taken from participants, and 6-8mls of peripheral blood was drawn to determine serum uric acid and HbA1c levels.

Results: A total of 150 participants were recruited, with 66% females, 34% males, and a mean (SD) age of 56.4 years. The mean (SD) duration of follow-up for diabetes was 10.3 years. Hypertension was a comorbidity in 65.3% of the participants, and obesity in 36%. The mean (SD) HbA1c levels were 7.76% and 42.7% had good glycemic control. Prevalence of hyperuricemia is at 19.3% in the study. The mean (SD) serum uric acid levels were 5.02mg/dl (299μmol/L). No correlation was found between hyperuricemia and duration of diabetes and glycemic control. Relationship between hyperuricemia and the variables of age, BMI and hypertension did not achieve statistical significance. Female gender achieved significance with a P value of 0.046.

Conclusion: There is a high prevalence of hyperuricemia at 19.3% in this study population especially in the females above the age of 40 years. Patients were on long-term follow-up for diabetes, the glycemic control was average to good. This forms a basis for regularly screening patients for serum uric acid levels in the clinics. Further studies with larger number of patients with diabetes are needed to

explore the relationship of hyperuricemia to other clinical and laboratory parameters.

Key words: Serum uric acid, Type 2 diabetes

Introduction

Uric acid is a product of the metabolic breakdown of purine nucleotides, and it is a normal component of urine. Hyperuricemia is defined as a serum urate level of 6.8 mg/dl (404μmol per liter) or more¹. The rising incidence and prevalence of hyperuricemia are probably related to the increased life expectancy of the population, increasing levels of obesity, sedentary lifestyles and change in dietary habits².

Type 2 diabetes mellitus consists of an array of dysfunctions characterized by hyperglycemia and resulting from the combination of insulin resistance, inadequate insulin secretion, and excessive or inappropriate glucagon secretion. Type 2 diabetes mellitus is less common in Non-Western countries where the diet contains fewer calories and daily caloric expenditure is higher. However, as people in these countries adopt Western lifestyles, weight gain and Type 2 diabetes mellitus are becoming virtually epidemic. Prevalence of diabetes is increasing worldwide. The International Diabetes Federation predicts that the number of people living with diabetes will rise from 366 million in 2011 to 552 million by 2030³.

It has been shown that serum uric acid is positively associated with serum glucose levels in healthy subjects⁴. Recent studies have demonstrated that uric acid levels are higher in subjects with Type 2 diabetes than in healthy controls⁵⁻⁸. Furthermore, an elevated serum uric acid level was found to increase the chances and predispose to developing Type 2 diabetes in individuals with impaired glucose tolerance⁹. Hyperuricemia has also been added to the set of metabolic abnormalities associated with insulin resistance and/or increased insulin

secretion in metabolic syndrome¹⁰. An elevated uric acid levels, as reported, often precedes the development of obesity, hyperinsulinemia, and diabetes¹¹.

Potential clinical consequences of hyperuricemia include gout, urate crystal deposition disorders, chronic kidney disease, nephrolithiasis and non-crystal deposition disorders such as hypertension and coronary artery disease.

The morbidity and mortality of diabetes is increased by hyperuricemia. It confers a poor prognosis on the diabetic complications. There is increased prevalence of diabetic peripheral neuropathy and it shows a significant correlation with increased UA levels¹². UA concentration has been shown to be associated with an increased severity of diabetic retinopathy in a study done over a three-year period in patients with T2DM¹³. Hyperuricemia is also associated with accelerated disease progression in the early stage of diabetic nephropathy¹⁴.

Significance of the study: Hyperuricemia is a serious yet forgotten test to be screened for and has been implicated in Type 2 diabetes. It is associated with poor glycemic control and diabetes-related complications including retinopathy, foot ulcers and deterioration in renal function. There is paucity of data on the prevalence of hyperuricemia amongst patients with Type 2 diabetes in Kenya which can be used in formulating local guidelines.

Objective: To determine the prevalence of hyperuricemia among ambulatory Type 2 diabetes patients at KNH and to correlate with duration of disease and glycemic control, and their clinical and demographic characteristics (age, sex, BMI and hypertension).

Materials and methods

This was a descriptive cross-sectional study conducted in the diabetes out-patient clinics at KNH. Patients aged 18 years and above were included, with a documented diagnosis of Type 2 diabetes, with normal kidney function tests and no dyslipidemias, who gave written informed consent. Patients on long-term diuretics (Thiazide diuretics as they are known to cause hyperuricemia) and steroids, on antimetabolite and chemotherapy drugs, pregnancy and lactating mothers, on uricosuric drugs and urate lowering agents were excluded. The sample size was calculated using the Daniel's formula and a minimum sample size of 150 was achieved.

Patients were recruited by simple random sampling. Data collection was done using a structured data collection tool and anthropometric measurements taken. Blood samples for serum uric acid and HbA1c levels were drawn and analysed in the KNH Biochemistry Laboratory using an automatic biochemistry analyser (COBAS INTEGRA 400/400 PLUS/800).

Study variables:

- ✓ Serum uric acid levels
 - o Hyperuricemia was defined as serum uric acid levels greater than 7.2mg/dl ($>428\mu\text{mol/L}$)
- ✓ Glycemic control - This was assessed by measuring glycated haemoglobin (HbA1c). HbA1c less than or equal to 7% was considered as good control, HbA1c between 7% to 8% was considered as moderate control and HbA1c greater than 8% as poor control.

Data analysis: Pearson product moment correlation was used to evaluate for any relationship between hyperuricemia and duration of diabetes and glycemic control. Pearson Chi-Square and Fischer exact tests was used for the different patient characteristics.

This study was carried out after a written approval had been issued by the Department of Clinical Medicine and Therapeutics, University of Nairobi, and KNH/UON Ethics and Review committee based at KNH.

Results

Table 1 shows the demographic characteristics of the 150 diabetic patients recruited into the study. The study population had a mean (SD) age of 56.47 ± 13.43 years and a median of 57 years with majority between the ages of 46 – 65 years at 52%. The population was predominantly females at 66% and most had attained primary school education at 45.3 years.

Table 1: Demographic information of the patients (N=150)

Characteristic	Frequency n (%)
Age group (years)	
18 – 25	1 (0.7)
26 – 35	7 (4.7)
36 – 45	26 (17.3)
46 – 55	36 (24.0)
56 – 65	42 (28.0)
66 – 75	26 (17.3)
76+	12 (8.0)
Sex	
Male	51 (34.0)
Female	99 (66.0)
Marital status	
Single	7 (4.7)
Married	122 (81.3)
Separated/Divorced	3 (2.0)
Widowed	18 (12.0)
Education level	
None	6 (4.0)
Primary	68 (45.3)
Secondary	54 (36.0)
Tertiary	22 (14.7)

Table 2 shows the clinical and anthropometric characteristics of the 150 study participants. The mean duration since diagnosis of diabetes was 10.3 years with majority having been on follow up for 1-10 years. The most common mode of treatment was oral hypoglycemic agents only in 47.3%.

The study population had comorbidities of hypertension at 65.3% whose mean blood pressure was at 140/78mmHg (± 20.8 mmHg) and obesity at 36%.

Table 3 shows the laboratory characteristics of the study population. Hyperuricemia prevalence is at 19.3% in the study participants. The mean (SD) serum uric acid

Table 2: Clinical and anthropometric characteristics of the study population

Clinical characteristics	All study participants	
	N	(%)
Duration since diagnosis of DM (years)	Mean (SD) 10.3 $\pm$ 7.8 years	Median 10.0 years
Duration of diabetes (years)		
1-10	87	58
11-20	51	34
21-30	7	4.7
31-40	5	3.3
History of hypertension		
Yes	98	65.3
No	52	34.7
Current diabetic medication		
Insulin injections	23	15.2
Insulin and oral hypoglycemics	55	36.7
Oral hypoglycemic agents only	71	47.3
None	1	0.7
BMI category		
Normal	37	24.7
Overweight	59	39.3
Obese	54	36.0

Table 3: Laboratory characteristics of the study population

Laboratory parameter	Mean $\pm$ SD (n = 150)	Median
HbA1c	7.76% $\pm$ 2.3	
Serum uric acid levels	5.02 $\pm$ 1.84 mg/dl (299 μ mol/L)	4.60 mg/dl (274 μ mol/L)
Categories of parameters	N	(%)
HbA1c category		
Good (< 7%)	64	42.7
Moderate (7 to 8 %)	32	21.3
Poor (> 8 %)	54	36.0
Serum uric acid level category		
Low (< 3.4 MG/DL / <202 μ mol/L)	16	10.7
Normal (3.4 – 7.2 MG/DL / 202 - 428 μ mol/L)	105	70.0
High (> 7.2 MG/DL / >428 μ mol/L)	29	19.3

level was 5.02 mg/dl (299 μ mol/L). Glycemic control was good as the mean (SD) HbA1c was 7.76% with 42.7% having a HbA1c below 7%.

Table 4 shows the relationship between serum uric acid levels and demographic data. Results show that there are no statistical differences between hyperuricemia

in respect to age (p = 0.067), BMI (p = 0.100), and history of hypertension (p = 0.315). Female sex is a risk factor for hyperuricemia in the study (p = 0.046). Serum uric acid levels had no correlation with duration of diabetes, r = 0.019, p = 0.816 and glycemic control p = 0.013.

Table 4: Correlation of selected characteristics with serum uric acid levels among the study participants

	Frequency n (%)			Total n (%)	P value
	Hypouricemia	Normouricemia	Hyperuricemia		
Age (years)					
18 – 25	1 (6.2)	0 (0.0)	0 (0.0)	1 (0.7)	0.067
26 – 35	0 (0.0)	7 (6.7)	0 (0.0)	7 (4.7)	
36 – 45	4 (25.0)	20 (19.0)	2 (6.9)	26 (17.3)	
46 – 55	5 (31.2)	21 (20.0)	10 (34.5)	36 (24.0)	
56 – 65	1 (6.2)	33 (31.4)	8 (27.6)	42 (28.0)	
66 – 75	3 (18.8)	18 (17.1)	5 (17.2)	26 (17.3)	
76+	2 (12.5)	6 (5.7)	4 (13.8)	12 (8.0)	
Sex					
Male	1 (6.2)	39 (37.1)	11 (37.9)	51 (34.0)	0.046
Female	15 (93.8)	66 (62.9)	18 (62.1)	99 (66.0)	
BMI					
Normal	6 (37.5)	28 (26.7)	3 (10.3)	37 (24.7)	0.100
Overweight	6 (37.5)	43 (41.0)	10 (34.5)	59 (39.3)	
Obese	4 (25.0)	34 (32.4)	16 (55.2)	54 (36.0)	
History of hypertension					
Yes	8 (50.0)	69 (65.7)	21 (72.4)	98 (65.3)	0.315
No	8 (50.0)	36 (34.3)	8 (27.6)	52 (34.7)	

Discussion

The study established that 1 in 5 patients with diabetes (19.3%) had hyperuricemia. Hyperuricemia was predominantly seen in females at 62.1% and obese study participants at 55.2%. Studies done in different countries give a prevalence ranging from 11.4 – 32% in Type 2 DM patients. The prevalence in our study is lower in comparison to what is reported in studies conducted in Egypt, Ethiopia and Nigeria but has a similar prevalence to the study done locally in Kenya^{6-8,15}.

The variation in prevalence can be attributed to differences in population profiles such as different dietary habits and choices, as well as geographical / environmental and genetic differences. Some of the differences observed in prevalence of hyperuricemia across in the above studies⁶⁻⁸ are attributable to the difference in sample sizes and cut off value for defining hyperuricemia used by the authors. Our study excluded patients with deranged renal function tests based on calculating eGFR, dyslipidemias and any drug, that would potentially influence serum uric acid levels. These exclusion criteria may have contributed to our low prevalence. In our study, hyperuricemia is defined as serum uric acid levels above 7.2mg/dl (428µmol/l). The mean (SD) age of our study population was 56.47 years (±13.4 years) and the mean (SD) duration of DM was 10.3 ± 7.8 years.

Ogbera *et al*⁸ used a cut off point of 7.0mg/dl for hyperuricemia, did not exclude dyslipidemias and used a large sample size of 601 patients. It has been shown that serum uric acid is positively associated with serum triglycerides and total cholesterol. Fouad *et al*⁷ also found a high prevalence, however he did not exclude patients with deranged renal function tests and used a large sample size of 986 patients. Patients with low eGFR tend

to have hyperuricemia due to poor excretion¹⁶. Woyesa *et al*⁶ also found a high prevalence rate of hyperuricemia at 33.8%, however his sample size was larger than our study. Majority of his sample population were obese and he did not exclude dyslipidemia. Rao *et al*¹⁷ found a low prevalence as he had a small sample size of 70 patients. Locally Sylvia *et al*¹⁵ found hyperuricemia in 44% of hypertensive patients attending Moi Teaching and Referral Hospital. She further looked into those with diabetes and found a prevalence of 18.2%. She had similar findings to our study as her diabetic patients with hyperuricemia were predominantly female, obese and in similar age bracket.

Obesity has been found to contribute to hyperuricemia¹⁸. BMI is highly dependent on the individual's genetic composition, dietary habits and level of physical activity. Majority of our population were obese and overweight at 75.3%. In the hyperuricemia group 89.7% were in the overweight and obese group. The mean (SD) BMI among the patients with hyperuricemia was 29.2 kg/m². This is similar to majority of the studies. Ogbera *et al*⁸ found a mean (SD) BMI of 28.9 kg/m² and Fouad *et al*⁷ found a mean (SD) BMI of 30 kg/m² in the patients with hyperuricemia. Locally Sylvia *et al*¹⁵ found a mean (SD) BMI of 30.2 kg/m² in the hyperuricemia patients and achieved statistical significance. Rao *et al*¹⁷ found a low prevalence, his study had lower number of obese participants. In our study we did not reach a statistical significance between serum uric acid levels and BMI, $p = 0.100$. Though we did not entirely screen for metabolic syndrome in our study, it seems like most of our patients would fall in this category; considering that the prevalence of obesity and metabolic syndrome is rapidly increasing in developing countries due to urbanization, unhealthy food options and physical

inactivity. Metabolic syndrome causes insulin resistance which enhances renal urate reabsorption via stimulation of urate-anion exchanger and/or the sodium dependent anion co-transporter in brush border membranes of the renal proximal tubule. Our population also needs to be screened for fructose consumption habits. The epidemic trend of obesity in recent years has also coincided with the increasing use of fructose especially in beverages. Fructose intake contributes to insulin resistance, impaired glucose tolerance, and hyperinsulinemia predisposing to hyperuricemia by increasing ATP degradation to AMP, a uric acid precursor and also de novo purine synthesis is accelerated¹⁹.

Hyperuricemia has been strongly associated with male gender^{6,7}. There was a female preponderance in the hyperuricemia group, 37.9% were males and 62.1% females, with a gender ratio of 1:1.6. This goes against what is known that gout is largely a male dominated disease. The difference can be explained by the possible reason that more females were recruited as they have a better health seeking behavior than the males. More females have diabetes in our setup, also proven by other studies looking into diabetes²⁰. The age of women was significantly higher as most of them were older than 50 years, and may have been menopausal losing the protective effect of estrogen, and majority were in the overweight and obese group. The same has been shown in the study done by Sylvia *et al*¹⁵ in Eldoret, who also had a female preponderance at 66% and hyperuricemia was seen in 71.1% of the females and is explained by the same possible reason of older age, and most being obese. Our study achieved a statistical significance between female gender and serum uric acid levels at $p = 0.046$.

Our study shows that majority of the patients with hyperuricemia were in the older age group, between the age of 46 and 65 years at 62.1% and is comparable to the other studies. All the other studies achieved a statistical significance between old age and hyperuricemia confirming that the prevalence of hyperuricemia is more with advancing age. Though our study did not achieve a statistical significance, $p = 0.067$. This is in keeping with the study done locally by Sylvia *et al*¹⁵ who found a mean (SD) age of 54 years and also did not achieve a statistical significance. The mean (SD) age of the overall population in our study was 56.47 ± 13.4 years. It is comparable to the age obtained by Ogbera *et al*⁸ in Nigeria who recorded a mean (SD) age of 59.9 years. However, Woyesa *et al*⁶ in Ethiopia reported a lower mean (SD) age of 49.8 years and Fouad *et al*⁷ in Egypt recorded a mean (SD) age of 47.9 years.

Hyperuricemia has been found to be prevalent in hypertension¹⁵. In our study, 65.3% had a documented diagnosis of hypertension with 72.4% being hypertensive in the hyperuricemia group. Only 34% of the patients had adequate BP control. It is also quite evident that diabetes and hypertension do co-exist in many of our patients. Diabetic patients with hypertension are more vulnerable

to both cardiovascular and renal complications compared to diabetic non-hypertensive patients; hence, BP control is paramount in this patient population. We excluded patients on Losartan due to its urate lowering effects and thiazide diuretics which increase serum uric acid levels. Our study did not achieve statistical significance between serum uric acid and hypertension, $p = 0.315$.

The mean (SD) duration of DM in our study is 10.3 ± 7.8 years. This is higher in comparison to the other studies. Ogbera *et al*⁸ reported a mean (SD) duration of 6.9 years and Woyesa *et al*⁶ reported a mean (SD) of 7.2 years. Longer duration of disease predisposes to a higher likelihood of diabetic complications predisposing to hyperuricemia and also requiring intensified treatment, such as use of injectable as a viable treatment option to achieve good glycemic control, this has been shown in the study that 53% were on insulin based therapy either as monotherapy or in combination with the oral drugs. The relationship of hyperuricemia with duration of diabetes needs more studies as the other studies done have found different results. Woyesa *et al*⁶ reported patients with duration of diabetes with less than 10 years had more hyperuricemia as compared to patients with a diagnosis of a longer duration. Fouad *et al*⁷ found the converse where patients with a diagnosis of 10 years and more had more hyperuricemia. Most of the patients with hyperuricemia in our study had a mean (SD) duration of more than 10 years. There was no correlation between serum uric acid levels and duration of diabetes $P = 0.816$.

Glycemic control was generally good at 42.7% having HbA1c below 7% based on the ADA criteria³. This shows improvement to other studies done, Omari *et al* (KNH 2013) found 29.2% with HbA1c below 7%; and Otieno *et al* (KNH 1998) found 39.5% of patients with HbA1c less than 8%. Patients with poor glycemic control are more likely to have hyperuricemia as compared to those with good glycemic control and this was found to be statistically significant in the other studies. We did not achieve a statistical significance in our study ($p = 0.013$) as the glycemic control was largely good and the population sample size was small. Poor glycemic control is associated with hyperinsulinemia that enhances uric acid reabsorption in the kidneys²¹.

Conclusion

- (i) We found a relatively high prevalence of hyperuricemia at 19.3% in our study population.
- (ii) Females have been shown to have a higher prevalence and those in the age group of 40 – 60 years should be routinely screened.
- (iii) Hyperuricemia has no correlation with duration of diabetes and glycemic control in the study.
- (iv) Hyperuricemia has no relationship with the variables of age, BMI and hypertension in the study. Only female gender achieved significance.

Study limitations

- (i) This was a cross-sectional study hence no causal inference or temporal association could be drawn. It would have been ideal to compare the serum uric acid levels obtained in our study with those generated from the local population; however, there is lack of locally generated data on serum uric acid levels.
- (ii) We were unable to investigate for other causes of hyperuricemia among our diabetic patients due to limited resources. Our study did not factor in genetics, which significantly affect the serum uric acid levels.
- (iii) This was a single center study with a relatively small sample size so these results may not be generalizable to the entire population of patients with Type 2 diabetes in Kenya.
- (iv) Patients included in the study are not representative of all the patients with Type 2 diabetes as confounding factors like deranged renal functions and dyslipidemias were excluded and the lack of a control group to compare with serum uric acid levels in the general population.

Recommendations

- (i) Studies should be conducted to determine serum uric acid levels in the normal population. This will show the prevalence of hyperuricemia, as well as give normal population values in the local population.
- (ii) Regular screening for serum uric acid levels in the patients on follow up in the diabetic clinic especially female patients in the age of 45 to 60 years.

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Corresponding author:

Dr. Fredrick O Otieno.

Email: fred.otieno@aku.edu

C-ANCA positive GPA with pulmonary involvement: a case report

Abdukarim S, Sokwala A, Ali SK, Otieno FO

Abstract

Granulomatosis with polyangitis (GPA) represents a rare cause of systemic vasculitis with relatively even fewer cases reported from Africa. The possible explanations for the relatively low incidence are thought to be because of possibly actual low prevalence in this population, low index of suspicion for the condition and under-diagnosis due to lack of diagnostic services. In this case report we present a 75 year old female with cytoplasmic anti-neutrophil cytoplasmic antibody (c-ANCA) positive granulomatosis with polyangitis with predominantly pulmonary involvement admitted with pneumonia and Acute Respiratory Distress Syndrome (ARDS) who transiently improved with immunosuppressive therapy, plasma exchange and rituximab but eventually succumbed due to septic shock.

Key words: C-ANCA, Pulmonary, Granulomatosis, Vasculitis.

Introduction

The incidence of vasculitis including GPA in Africa and Kenya is unknown, though thought to be relatively rare as it is globally. It is however on the rise with improving diagnostic services and standardization of diagnosis criteria. Cases remain largely unreported or undiagnosed due to lack of diagnostic services and financial constraints¹. In addition, guidelines for diagnostics and treatment are largely derived from studies from Western sources.

GPA represents a small-medium vessel vasculitis as per the Chapel-Hill classification of vasculitides². It is one of the Antinuclear Cytoplasmic Antibodies (ANCA) Associated Vasculitis (AAV). It is characterized by necrotizing granulomatous inflammation involving the upper and lower respiratory tracts and a necrotizing vasculitis affecting small to medium vessels. GPA may present with symptoms of upper and lower respiratory

tract involvement with or without renal involvement with glomerulonephritis.

The American College of Rheumatology (ACR) criteria for the diagnosis of GPA require two of the following³:

- (i) Features of nasal or oral inflammation
- (ii) Abnormalities on chest radiography showing nodules, infiltrates or cavities
- (iii) Abnormally on urinalysis – microscopic haematuria/proteinuria
- (iv) Biopsy evidence of granulomatous inflammation

GPA is associated with PR3-ANCA antibodies which are positive in 82-94% of cases⁴. Up to 10% may however have antibody negative GPA⁵.

Establishing a diagnosis early is key as it causes early initiation of treatment that can be life and organ saving. Treatment involves immunosuppressive therapy.

When untreated, GPA poses a high mortality with a mortality rate of up to 90% at two years. Treatment studies have reported mortality rates ranging from 12 to 28% at 7 to 8 years' 6-8 to 24 to 44% at 4 to 10 years 9-13. Causes of mortality include infections related to use of immunosuppressive therapy, organ effect (lung or renal) and cardiovascular disease^{6, 7}.

Case presentation

A 75 year old female presented to our facility with a history of dyspnea for 5 days associated with fevers and a productive cough. She denied any chest pain, rashes or a travel history.

She had been on prednisolone and azathioprine for c-ANCA positive GPA as an outpatient with no recorded flares or prior hospitalizations. The diagnosis was made 4 years prior on the basis of long standing cough and dyspnea with CT chest revealing nodular lesions with biopsy findings of non caseating granulomas. Her c-ANCA test was positive. She had been treated for pulmonary tuberculosis prior to the diagnosis of GPA with no positive microbiological studies and

persistence of her symptoms. She was also reported to have deterioration in her vision and managed for scleritis. She was not known to have any other medical comorbidities. She was lost to follow up however, last seen 7 months prior to her admission.

On initial assessment her vitals were: BP 110/70 mmHg pulse rate 96/minute temperature: 38.5 degrees celsius respiratory rate: 20/minute SPO2: 90% on non rebreather mask at 15 liters/minute. She had no peripheral edema. Her examination was remarkable for bilateral coarse crepitation on respiratory auscultation.

Her initial diagnostic evaluation was as follows – haemoglobin 11.9 g/dl, WBC count 8.58, neutrophils 88%, platelet count 265. Sodium 132 mmol/L, creatinine 88 mmol/L BUN 8.1 mg/dL. Procalcitonin was elevated at 6.51 ng/ml and C-Reactive Protein was 291 mg/L. Arterial blood gas analysis revealed respiratory alkalosis with hypoxemia. C-ANCA was tested positive and p-ANCA negative. A urinalysis at the time revealed haematuria and mild proteinuria. CT of the chest revealed bilateral perihilar and lower lobe consolidations and patchy upper lobe opacities bilaterally. Sputum studies including ZN stain and geneXpert for tuberculosis were negative. PCR for PCP was also negative. Tests for HIV/hepatitis B/hepatitis C were negative.

She was admitted to the High Dependency Unit (HDU) and started on antibiotics empirically. Was also initiated on high dose steroids and continued on the azathioprine. She had worsening respiratory distress and type 1 respiratory failure requiring intubation and mechanical ventilation by her fifth day of admission. Her course was complicated by a right sided pneumothorax detected after 2 days of ventilation for which she had a chest tube inserted with resolution of the pneumothorax. She was commenced on plasmapheresis on the 8th day of admission and received four sessions of the same (days 8, 10, 15 and 18 of admission). She developed oliguric acute kidney injury on her 13th day of admission requiring 2 sessions of dialysis. Her renal function recovered progressively with normalization of her creatinine and good urine output. She received induction with rituximab at 3 weeks given her first organ-threatening relapse and she demonstrated clinical improvement with improving ventilator requirements as well as neurological status. She however later developed septic shock with positive blood culture for *Acinetobacter baumannii* and succumbed despite adequate treatment.

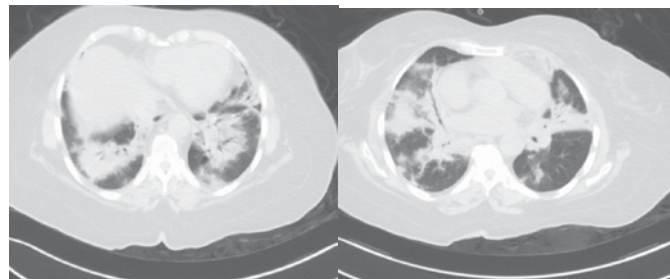
Figure 1: Chest radiograph on admission



Figure 2: After immunosuppressive treatment/antibiotics



Figure 3: CT scan of the chest at admission



Discussion

GPA categorized as a small-medium vessel, ANCA associated vasculitis is thought to be relatively rare with overall incident rates of AAV in Europe reported to be between 13-20/million. There are no local studies on prevalence or incidence in Africa. A literature review revealed no locally reported cases in Kenya. Some of the reasons behind relatively fewer cases being reported locally include: A truly lower prevalence, lack of suspicion for the condition among physicians and lack of diagnostic services. In addition, the clinical features such as constitutional symptoms with respiratory symptoms may mimic more prevalent infectious conditions such as tuberculosis, as was the case in the patient. The incidence of GPA is known to increase with age⁸. Our patient had the diagnosis first made at 71 years of age.

GPA may present with nonspecific constitutional symptoms, symptoms of upper/lower respiratory tract involvement or renal involvement with glomerulonephritis. In two studies in Tunisia on patterns in GPA, the most common symptoms at presentation were ear, nose and throat symptoms followed by pulmonary symptoms⁹. Our patient initially presented with chronic cough and dyspnea. She also developed ocular symptoms which are known to occur¹⁰.

The diagnosis of GPA is based on clinical, imaging and laboratory criteria. Early diagnosis is vital as it enables institution of early treatment that can be life and organ sparing. In addition to clinical symptoms/signs, a biopsy of affected organ demonstrating characteristic histological features plays a key role in diagnostic work up. Where suspicion is high however, diagnostic evaluation shouldn't delay treatment. ANCA testing should be done in any patient suspected of having vasculitis. Positivity rates for c-ANCA in GPA are reported to be between 82-94%⁴. Locally, a Tunisian study by Ben Ghorbel *et al*⁹ determined c-ANCA to be positive in 90% of the 30 patients in the case series.

Treatment of GPA largely involves immunosuppressive therapy. Initial immunosuppressive therapy in patients with a life or organ threatening presentation involves glucocorticoids in combination with either rituximab or cyclophosphamide¹¹. In addition, plasma exchange may be used in patients with rapidly worsening renal function or severe renal dysfunction¹², anti-glomerular basement antibody positivity^{13,14} or pulmonary haemorrhage^{15,16}. On admission and during her hospital course she received glucocorticoid therapy, rituximab and plasmapheresis with demonstrated clinical improvement and radiologic improvement in the lung infiltrates. Despite the improvement she later developed septic shock with *Acinetobacter baumannii* cultured from blood.

Conclusion

While c-ANCA granulomatosis with polyangitis is relatively rare in our local setting, it is prudent to have a high index of suspicion for the condition for appropriate and timely management. In this case report we present a 75 year old female on follow up for c-ANCA positive GPA admitted with a relapse with predominantly pulmonary involvement and concurrent community acquired pneumonia with severe ARDS who improved on treatment with immunosuppressive therapy, rituximab and plasmapheresis and antibiotics but eventually succumbed due to septic shock

Conflict of interest: None

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