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# Contemporary data on musculoskeletal manifestations of chikungunya infection and association with osteoporosis: a narrative review

*Y.H. Mogos[1], J.A. Balushi[2], N.A. Dermenjian[3], R. Mahawa[4], R.F. Worku[5]*

[1]Orotta School of Medicine, Waterloo, Canada
[2]University College Dublin, Dublin, Ireland
[3]Yerevan State Medical University, Los Angeles, CA, USA
[4]Government Medical College Amritsar, Punjab, India
[5]St Paul's Hospital Millennium Medical College, Addis Ababa, Ethiopia

***ABSTRACT:***

The chikungunya virus (CHIKV) is an alphavirus transmitted to humans mainly through the bite of infected *Aedes aegypti* and *Aedes albopictus* mosquitoes. It has recently resurfaced in various parts of the world, triggering widespread outbreaks. CHIKV infection results in chikungunya fever (CHIKF), a temporary febrile illness typically enduring for 7-10 days. Symptoms include rash, fatigue, severe polyarthralgia affecting the hands and feet, and myalgia. Chronic CHIKF, lasting more than 3 months, affects over 40% of those infected, leading to arthritic changes such as bone erosion, enthesopathies, periostitis, and persistent joint pain.

We conducted a narrative review to discuss the musculoskeletal manifestations of CHIKV infection as well as its effects on bone health and to explore current data linking CHIKV infection with osteoporosis. We performed a comprehensive literature search including peer-reviewed publications.

Patients with chronic infection develop an incapacitating arthritis that may persist for months to years and thereby impose a burden on the population in terms of disability-adjusted life years (DALY). A recent increase in outbreaks may be related to virus evolution, globalization/international travel, and climate change, thus potentially turning CHIKV into a major global health threat. Several studies have elucidated the impact of CHIKV infection on bone health and its correlation with arthritic changes. Various cellular and molecular factors contribute to bone erosion during chikungunya virus infection. In CHIKV infection and other arthritogenic alphavirus infections, inflammatory processes marked by the production of interleukin-6 (IL-6), monocyte chemoattractant protein-1 (MCP-1), and interleukin-1 (IL-1), along with an elevated receptor activator of NF-kB ligand/osteoprotegerin (RANKL/OPG) ratio, promote the formation of osteoclasts from monocytic precursors. Consequently, this leads to increased bone resorption and bone pathologies.

The literature on osteoporosis and Chikungunya fever is a promising area of research with implications for clinical practice and scientific understanding. Further research in this field has the potential to improve outcomes for individuals affected by these conditions and expand our knowledge of the relationship between viral infections and bone health.

***Keywords:*** Chikungunya virus, Arthritogenic alphaviruses, Osteoporosis, Arthritis, Bone resorption.



Corresponding Author: YH Mogos, MD; e-mail: mogosyohana@gmail.com

## INTRODUCTION

Chikungunya is a word of Tanzanian origin, meaning "disease that bends up the joints"[1]. It is a mosquito-borne alphavirus discovered in Tanzania in 1952, where the transmission was associated with a Sylvatic cycle by the *Aedes* mosquitos[2]. However, different transmission patterns have been observed elsewhere. For example, the chikungunya virus (CHIKV) in Asia follows an urban cycle[3]. Today, a vaccine is available that could help control the spread of the virus[4]. In an outbreak that occurred in 2006 in India, it was reported that 775,000 people were infected and 237 died[5]. Krishnamoorthy et al[6] studied the economic impact of this epidemic, estimating a loss of approximately 3 million USD. Additionally, 25,588 days were lost due to the illness, with 30.9% attributed to Disability-adjusted life years (DALYs) and 69.1% to persistent arthralgia.

Chikungunya virus infection is characterized by the sudden onset of fever and various symptoms such as skin rash, arthralgia, myalgia, joint edema, backache, retro-orbital pain, photosensitivity, nausea, vomiting, diarrhea, abdominal pain, anorexia, and others[7]. A systematic review by Rodríguez-Morales et al[8] demonstrated that 40.2% of patients experienced chronic inflammatory rheumatism. This contributes to the pathophysiology that classifies CHIKV as an arthritogenic virus, causing the triad of arthralgia, arthritis, and myalgia[9]. Arthralgia persists in 37% of patients, with long-term complications reported in 30% of cases[10]. The virus targets osteoblasts, muscle cells, and various other cell types through macropinocytosis. This was confirmed when the use of macropinocytosis inhibitors led to a reduction in viral load[11]. The etiology is not entirely understood, and there are many proposed theories on how chikungunya infection affects bone health. A study[12] demonstrated that CHIKV infects human synovial fibroblasts, making them susceptible to the upregulation of arthritis-inducing genes like regulated upon *activation, normal T cell expressed and presumably secreted/C-C motif chemokine ligand-5* (*RANTES/CCL5*), which also accelerates osteoporosis-like symptoms. Another proposed theory is the increased expression of proinflammatory cytokines like interleukin-6 (IL-6), monocyte chemoattractant protein-1 (MCP-1), and IL-8, which induce osteoclast differentiation, altering the osteoblast-osteoclast balance[13]. Osteoclasts produce acids, matrix metalloproteinases, and cathepsin K, which cause bone resorption and matrix degradation[14]. Furthermore, due to the imbalance caused by the CHIKV, osteoblasts do not compensate for this matrix loss, potentially leading to osteoporosis. The aim of this review is to discuss the available data on the epidemiology and clinical manifestations of Chikungunya infections with an emphasis on the effect CHIKV has on bone health and potential implications in the development of osteoporosis.

## EPIDEMIOLOGY

Chikungunya virus belongs to the family *Togaviridae*, genus *Alphavirus*, and is primarily transmitted to humans through the bite of infected *Aedes aegypti* and *Aedes albopictus* mosquitoes. Vertical CHIKV transmission has also been reported in different outbreaks[15-17]. Because *Aedes aegypti* cannot withstand cold climates, its distribution is limited to South America, Central America, some US countries, Sub-Saharan Africa, Southeast Asia, Australia, China, and some European countries[18]. *A. albopictus* has a wider geographical distribution, being found in subtropical and temperate climates in addition to being able to survive through cold winters[19]. Both *A. aegypti* and *A. albopictus* bite mainly during the day, reducing the role of insecticide-impregnated bed nets in disease control. In addition to CHIKV, both *A. aegypti* and *A. albopictus* are known vectors of several other viruses, including yellow fever virus, dengue virus, and Zika virus.

CHIKV was first recognized as a human pathogen after its isolation from the serum of an infected patient during an outbreak in Tanzania in 1952[1,2,20]. Outbreaks of chikungunya, however, can be traced back to as early as 1779[21,22]. The virus is majorly endemic in tropical and subtropical regions of Sub-Saharan Africa and Southeast Asia, with subsequent epidemics occurring in the latter half of the twentieth century. Phylogenetic analysis traces the virus's origin back to Africa 500 years ago, while the first reported transmission in Asia occurred in the Philippines in 1954[23-25]. The lineage was divided into two major strains: the West African (WA) strain responsible for small focal outbreaks in West Africa, also referred to as the sylvatic cycle, and the East/Central/South African strain (ECSA), which contributed to other urban epidemics[7]. This cycle involves rural enzootic transmission between various sylvatic *Aedes* mosquitoes, such as *Aedes furcifer* and *Aedes africanus*, and animal reservoirs, with nonhuman primates acting as the main reservoir host[3,26]. In contrast, the ECSA strain is associated with urban epidemics and does not rely on nonhuman primates or a sylvatic cycle for its maintenance. Instead, similar to dengue and Zika viruses, it can be transmitted from human to human[27]. Consequently, the urban transmission cycles of CHIKV, particularly in densely populated tropical areas, often result in large outbreaks.

The most notable outbreak of the ECSA strain, with an estimated six million cases, was reported in 2004 in Kenya, comprising areas beyond the original historical range of the virus and affecting several islands in India, the Indian Ocean, and Southeast Asia. In 2011, CHIKV was reported for the first time in the Pacific Island region of New Caledonia[7]. In 2013, the first local transmission of the virus in modern history was reported in the Western Hemisphere on the Caribbean Island of French St. Martin[28]. The first reported outbreak of the virus in the Americas was in 2013, which was attributed to the transmission of the virus from the Asian lineage[29].

According to Fred et al[30], the risk factors for disease burden for CHIKV were more contextual in origin as compared to individual determinants. The main predisposing factors were found to be history in neighborhood and household, low socio-economically disadvantaged area, occupational inactivity, low altitudes of dwelling, poor knowledge of CHIKV transmission, vector-friendly neighborhoods and obesity.

## CLINICAL MANIFESTATIONS

Most symptomatic cases typically have an incubation period of 2-12 days[31,32]. The most characteristic features include high-grade fever with arthralgia and rash. Arthralgia and arthritis are reported as one of the most debilitating presenting symptoms, both in adults and children. The arthralgia is typically polyarticular and symmetric, mainly affecting distal joints. The most commonly affected joints are the wrists, phalanges, shoulders, elbows, ankles, knees, feet, and hips. The articular symptoms like pain may vary in intensity but not in anatomical positions. Patients can experience constant or intermittent pain in the affected joints. Vertebrae, temporomandibular joints and sternoclavicular joints are typically spared. Patients can also suffer from edema in the smaller affected joints like interphalangeal joints, wrists and ankles[33].

The rash of CHIKV is described as a generalized morbilliform maculopapular rash with normal islands of intervening skin, which characteristically spares the face. It develops within 3-4 days of the onset of fever and tends to subside in about a week without any sequel. Centrofacial pigmentation involving the nose is also another commonly encountered finding[34]. Dengue fever and Zika virus, although more commonly asymptomatic, can also cause skin rash ranging from mild erythema to a pruritic, macular rash with small circular islands of spared skin classically described as "isles of white on a sea of red"[35]. Because of the multiple overlapping symptoms and geographic area of distribution, dengue fever, Zika virus, and other similar rash-causing arboviruses like the Ross River virus should be considered as the top differential diagnosis for chikungunya fever (CHIKF)[36].

The most common complication involves the central nervous system, causing encephalopathy[37,38]. According to a study conducted in Reunion Island[39], the estimated cumulative incidence rate for chikungunya-associated encephalitis was 8.6 per 100,000 people during an outbreak, which led to a 2-fold increased incidence of all encephalitis in the region. Gastrointestinal symptoms like abdominal pain and nausea have also been reported in infected patients. Mild hepatitis also occurs as a clinical manifestation in some patients[40].

Chikungunya virus is also reported to cause some rare extra-articular manifestations like pericarditis, cardiac tamponade, myocarditis, and dilated cardiomyopathy, with heart failure reported as the most common cardiac manifestation[34]. The most commonly reported ocular manifestation is acute non-granulomatous or granulomatous anterior uveitis[41,42]. Other frequently repeated ocular manifestations comprise retinitis and exudative retinal detachment[42,43]. Rare neurological disorders associated with CHIKV are myelopathy, myelitis, acute disseminated myeloencephalitis, Guillain-Barre syndrome, stroke, febrile seizures, isolated cranial nerve palsies, and memory deficits[44]. Renal complications associated with CHIKV have also been reported in patients with other renal comorbid conditions, acute interstitial nephritis and tubular injury being the most commonly reported renal manifestations[34].

Chronic manifestations of CHIKV in the musculoskeletal system are quite common, but the pathogenesis is still poorly understood. Inflammatory polyarthritis has been reported as the most common long-term sequelae that occurs after chikungunya infection[40]. According to Schilte et al[45], more than 60% of patients suffered from arthralgia even 36 months post-acute infection. Long-term arthralgia typically involves more than two different joints, with hands, ankles, wrists, and knees being the most commonly affected locations. Kumar et al[46] also described chikungunya as an emerging and re-emerging febrile disease with debilitating long-term sequelae of arthralgia and myalgias persisting for years in 10-60% of patients.

Tritsch et al[47] reported a high prevalence of continued self-reported joint pain in patients three years post chikungunya infection, characterized in over half of the cases by relapsing-remitting symptoms, mild to moderate stiffness in three-fourths patients after a period of immobility and morning stiffness in over one third. Most patients described the pain as intermittent with recurrence, whereas 22% experienced constant pain with changes in intensity. Exercise was reported to be the most common provoking factor of pain. Patients experienced joint stiffness, which significantly impacted their physical activity.

## EFFECT OF CHIKUNGUNYA VIRUS ON BONE HEALTH

The first line response to chikungunya infection is the activation of the innate immune response[48]. Of the innate arm of the immune response, the role of natural killer (NK) cells, macrophages and dendritic cells has been elucidated in detail[49]. However, the involvement of neutrophils, eosinophils and other components of the innate immune system requires further exploration[49].

The first encounter of CHIKV after inoculation is with cells in the skin, primarily dermal dendritic cells, fibroblasts, and dermal macrophages, with dermal fibroblasts being particularly susceptible[50]. *In situ* replication of the virus within these cells leads to the production of chemoattractants, which attract addi-

tional cells of the innate immune system[50]. Among the proinflammatory cytokines produced by the incoming inflammatory cells, IL-1, IL-6, TNF-α and INF-α are particularly noteworthy[50]. These cytokines play a crucial role in defending against CHIKV infection. However, their impact can be both protective and pathogenic, which warrants further exploration[51].

After antigen presentation, the humoral and cell-mediated adaptive immunity is activated and results in the initiation of pathogen-specific memory responses[48]. Both the humoral and cell-mediated response are necessary for effective elimination of the virus[49]. However, these responses seem to be responsible for the clearance of the infection as well as pathological changes observed in target tissues[52]. Evidence from animal models shows that in the absence of the adaptive immunity response, higher levels of viremia and persistence of infection are seen along with reduced musculoskeletal manifestations[52]. The roles of both T and B lymphocytes remain unclear in chronic infection with CHIKV; however, evidence has characterized their involvement in the acute phase of infection.

$CD8^+$ T lymphocytes are responsible for the destruction of infected cells and mark early-stage CHIKV infection indicated by their early detection in peripheral blood after symptom onset[52], while $CD4^+$ T lymphocytes appear towards the end of the acute stage of infection[49,52]. Even though $CD8^+$ T lymphocytes increase in number early on and help clear the viremia, they do not protect against CHIKV-associated pathologies, which have been explained by sustained antigen presentation leading to cellular exhaustion and anergy[53,54]. Unlike $CD8^+$ T lymphocytes, which are yet to be implicated as a contributing factor for musculoskeletal manifestations of CHIKV infection, there is evidence from multiple studies[50-54] that suggest $CD4^+$ T lymphocytes aid and abate in the pathogenesis of joint swelling and pain. Despite this, $CD4^+$ T lymphocytes remain crucial in driving the antibody response against the virus[54].

Potently neutralizing antibodies (NAbs) block infection at multiple steps of the virus life cycle, including entry and release. The initial IgM response is followed by class switching to IgG within one week of symptom onset[52]. Early appearance of IgG response coincides with protection against chronic CHIKV infection[48]. Although CHIKV-induced symptoms usually resolve in patients within two weeks, approximately 30-40% of these patients develop chronic arthritis, which can be due to inefficient viral clearance or persistent immune response in patients[50,55,56]. The majority of the antibodies produced against CHIKV target the E2 envelope glycoprotein, which opens an interesting entry point for vaccine research[49]. Venugopalan et al[51], 2014 and Fox and Diamond[52], 2016 have shown that during the early stages of the disease, cytokines interferons (INFs) -α, -β, -γ, IL-1β, C-X-C motif chemokine 10/interferon γ-induced protein 10 kDa (CXCL10/IP-10), and chemokine (C-C motif) ligand 2/monocyte phemoattractant proteins (CCL2/MCP-1) dominated the inflammatory scene. As the disease progresses, cytokines such as IL-4 and IL-13 become more prevalent. Strong TH2 cytokine response (IL-4, -6, -13) was associated with prolonged persistence of musculoskeletal symptoms[49].

When we look at how these inflammatory changes and cascades set off by CHIKV infection relate to osteoporosis, it becomes crucial to understand that osteoporosis has now come to be viewed as a condition with a multifactorial etiology of which chronic inflammation is gaining popularity[57]. This contrasts with previous beliefs that osteoporosis was solely an endocrine disorder. Several hormones, growth factors, inflammatory mediators and other cell signaling molecules are involved in the regulation of osteoblasts and osteoclasts, the two cells whose interaction is integral for the balance between bone formation and resorption. Of the inflammatory factors, IL-1, IL-6, IL-17 and tumor necrosis factor-α (TNF-α) stimulate osteoclast differentiation and proliferation[57]. Additionally, IL-1, IL-6, and TNF-α have a cumulative effect on bone loss by inhibiting osteoblasts. On the other hand, IFN-γ, IL-3, IL-4, IL-10 and IL-12 inhibit osteoclasts, which tip the favor towards bone formation. Comparing Th1 and Th2 lymphocyte responses to their effect on bone loss, Th1 was previously thought to be osteoporotic, while Th2 cells are bone protective. However, current evidence suggests that Th1 cells have a dual but opposing effect on bone remodeling mediated by IFN-γ and TNF-α[58]. The anti-inflammatory regulatory T lymphocytes directly suppress osteoclast maturation, which indicates their bone protective role. On the other hand, it has been reported that $CD8^+$ T lymphocytes produce osteoprotegerin (OPG), inhibiting osteoclastogenesis[58].

All the above-mentioned data show the complex interaction between inflammatory cells and bone homeostasis. However, the overall effect seems to tip in favor of bone resorption. Chikungunya virus infection has been associated with altered bone formation and function, leading to changes in bone mineral density (BMD). Chen et al[59], 2014 provided evidence of CHIKV-induced bone loss in mice infected with the virus coupled with evidence that Bindarit [inhibitor of Monocyte Chemoattractant Proteins (MCP) expression] protected against this demonstrated bone loss. Two years later, Goupil et al[60], 2016 demonstrated the lack of significant differences in measurements in bone volumes between CHIKV-infected mice and control. The difference between the two findings was attributed to the different ages of mice used for the experiments. Javelle et al[61] also stated that there is no evidence of chikungunya infection inducing or worsening osteoporosis, except after prolonged courses of treatment with systemic corticosteroids.

More recent studies, such as Roy et al[62], 2019 discussed the influence of chikungunya infection on bone marrow-derived mesenchymal stem cells (BMMSCs) and osteogenic cells *in vitro* and *in vivo*. The study demonstrated that CHIKV can infect BMMSC, leading

to decreased alkaline phosphate activity and reduced calcium deposition in osteogenic cells. The infection impairs osteogenic differentiation of BMSCs, decreases *runt-related transcription factor 2* (RUNX2) gene expression (a master transcription factor for osteogenesis), and impairs the function of osteogenic cells. This mechanism can be an explanation for observed bone pathologies arising from chikungunya fever. However, further studies are required to clear up these conflicting findings and to elucidate the role of CHIKV on bone remodeling.

## DIAGNOSTIC TECHNIQUES AND DIFFERENTIAL DIAGNOSIS OF CHIKV INFECTION

Chikungunya fever is predominantly a clinical diagnosis, which is undertaken with consideration of epidemiologic and laboratory data. Nonetheless, laboratory confirmation is necessary to differentiate between several disorders with similar presentation, such as malaria in endemic areas, dengue fever, and other alphaviruses such as Zika virus and Ross River virus. During the acute phase of viral replication and for up to 5-10 days following the onset of symptoms, detection of viral nucleic acid in serum samples is the ideal way.

Following the acute phase, confirmation of infection relies on molecular assays, including rapid and sensitive techniques targeting viral components such as real-time loop-mediated real-time polymerase chain reaction (RT-PCR) and real-time TaqMan RT-PCR assay targeting the envelope *E1* gene or the non-structural *nsP1* gene and more recently, a one-step SYBR green-based real-time assay targeting the non-structural *nsp2* gene, in addition to conventional RT-PCR[63-67]. These molecular assays serve as initial tests for detection until an antibody response is detectable[68]. Subsequently, detection of CHIKV-specific immune response is achieved through serological methods such as enzyme-linked assays (ELISA), indirect immunofluorescence assays (IFA), hemagglutination inhibition (HI), and micro-neutralization (MNt), capable of distinguishing between IgG and IgM. IgM antibodies can be detected as early as 2-3 days after symptom onset. They may remain detectable for several weeks to 3 months, while CHIKV-specific IgG typically appears shortly after IgM antibodies and can persist for years. Various in-house ELISA techniques utilizing whole antigen or recombinant capsid or envelope antigens have also been described[69-71].

Differential diagnoses of chronic CHIKV infection, which occurs in over 40% of patients, include rheumatoid arthritis and systemic lupus erythematosus. Concomitant disease presentation is possible, and CHIKV infection in patients with RA has been shown to induce and exacerbate existing joint inflammation. Musculoskeletal imaging [including radiography, ultrasound, and magnetic resonance imaging (MRI)] plays a crucial role in evaluating the severity and extent of disease in the chronic phase. Radiographic findings may include periarticular osteopenia, osteoarthritis, soft tissue swelling, and rarely marginal erosions[72]. Ultrasound and MRI can reveal tenosynovitis involving the small joints of the fingers, joint capsule bulging, wrist effusions with incompressible synovial thickening, finger flexor tenosynovitis, cellulitis, wrist extensor tenosynovitis, and thickening of the median nerve[72-74].

## CLINICAL MANAGEMENT AND IMPLICATIONS

Current strategies for managing patients with CHIKF include pharmacologic and nonpharmacologic approaches. Literature suggests that cryotherapy, rehabilitation, and psychological support are very important during all stages of the disease to manage pain among patients[75]. The guideline for the pharmacological management of chikungunya recommends the use of medications such as dipyrone, paracetamol, non-steroidal anti-inflammatories (NSAIDs), corticosteroids, codeine, and morphine in the management of musculoskeletal pain, and use of methotrexate, chloroquine, and sulfasalazine in patients with chronic pain. Non-pharmacologic treatments, such as physiotherapy, orthoses, and acupuncture, are also highlighted as methods to reduce pain and musculoskeletal damage[76]. Guaraldo et al[77] emphasized the array of therapeutic options used in the management of the disease. These include chloroquine derivatives, disease-modifying anti-rheumatic drugs (DMARDs), biologic DMARDs, and medications for neuropathic pain. However, the literature suggests that the treatment efficacy remains inconclusive and is lacking evidence-based recommendations[78]. To explore potential treatments for chikungunya fever, host factors should be considered as targets for antiviral medications. The focus should be on drugs that can be effective at multiple stages of the CHIKV life cycle[79]. Additionally, an integrated approach combining pharmacological and nonpharmacological management is crucial for optimizing patient outcomes[75,76].

In resource-limited settings, where access to pharmacologic treatments may be restricted, nonpharmacologic approaches such as specific physiotherapy and homeopathic medicines become viable alternatives. These natural treatment options provide patients with a variety of methods to manage both acute and chronic symptoms effectively. The first study using a variety of homeopathic remedies for chronic CHIKV-associated arthritis, conducted by Wadhwani[80] in 2013, revealed a 90% resolution rate of chronic arthritis symptoms after an average of 32.5 days. Other literature suggests coconut water and turmeric can be used for their detoxifying and anti-inflammatory properties, grapes with cow's milk to reduce pain and fever, and olive oil with vitamin E for rashes[81]. Additionally, supplementation with low-impact aerobic exercise and light massage is known to relieve chronic joint pain.

Research and clinical practice for CHIKF presents several challenges. One of these challenges is the absence of specific treatment[82]. Also, understanding the complex pathogenesis and factors that can influence viral persistence and the development of chronic symptoms is considered a significant challenge. Diagnosis remains challenging due to the need for laboratory tests that may take time to yield results. Literature also emphasized the need for improved diagnostic methods that can effectively differentiate chikungunya from diseases with overlapping symptoms like Zika, Dengue, and Mayaro viral infections[82]. Current treatment consists of symptomatic management, hydration, and rest. Chronic symptoms arising after disease carry a huge burden for patients and healthcare. Minimizing the transmission risk by targeting the breeding grounds of *Aedes* mosquitoes and developing effective vaccines and antiviral treatments thus become crucial.

## CONCLUSIONS

The chikungunya virus is emerging as a global public health concern, with recent increases in outbreaks linked to virus evolution, globalization, international travel, and climate change. It has the ability to cause chronic, inflammatory, and debilitating arthritis. Multiple studies have demonstrated the impact of CHIKV infection on bone health. Research suggests that the inflammatory response triggered by CHIKV can lead to bone loss. However, to date, there is no evidence suggesting that CHIKV infection induces or exacerbates osteoporosis. While osteoporosis has been extensively explored in terms of global prevalence, risk factors, and treatment strategies, the direct association between chikungunya infection and osteoporosis remains primarily underexplored[83]. Various factors such as age, sex, genetic predisposition, low body mass index, and hormonal imbalances could potentially contribute to the increased risk of osteoporosis post-CHIKV infection[84]. Additionally, the prolonged joint pain and immobility caused by CHIKV infection can further exacerbate bone loss. The debate in this review revolves around the extent to which post-CHIKV osteoporosis is a direct result of the virus or a combination of factors, including lifestyle and pre-existing conditions.

Identifying the impact of the CHIKV virus on bone health is a crucial step to allowing early screening and treatment of osteoporosis in patients recovering from CHIKF. This becomes significant as it can lead to improved quality of life and reduced healthcare costs for individuals affected by these conditions. Furthermore, research on osteoporosis and CHIKF has the potential to contribute to our understanding of the immune system's role in bone health. By investigating how viral infections like CHIKV impact bone metabolism, researchers may discover new pathways and targets for therapeutic interventions in osteoporosis and other bone-related diseases. Potential areas of further research include longitudinal studies to establish a causal relationship between CHIKF and osteoporosis, as well as investigations into interventions to prevent or reduce bone loss in individuals with a history of CHIKF.

However, a major obstacle to diagnosing osteoporosis in regions where CHIKV is predominantly endemic is the limited access to dual-energy X-ray absorptiometry (DXA) scanning, the gold standard diagnostic modality. Insufficient access to DXA scanning facilities poses a significant barrier in many resource-limited countries. In these settings, non-specialist methods of fracture risk assessment can be utilized. One such tool is the FRAX® tool (https://frax.shef.ac.uk/FRAX/), which evaluates the risk of fragility fractures in patients by calculating the 10-year probability of hip or major osteoporotic fractures. This tool is based on individual patient models correlating the fracture risks associated with clinical risk factors as well as bone mineral density (BMD) at the femoral neck. The FRAX® models were developed by studying population-based cohorts from Europe, North America, Asia, and Australia. Similarly, studies on age-, sex- and ethnicity-specific hip fracture incidence rates in South Africa have been used to calibrate both a South African fracture risk assessment tool called FRAX™, and additional FRAX calibration has been accomplished based on hip fracture incidence data from Botswana, Ethiopia, and Tunisia[85-89]. The validity of these new FRAX tools in other resource-limited settings needs to be ascertained through further research.

In conclusion, the literature on osteoporosis and chikungunya fever is a promising area of research with implications for clinical practice and scientific understanding. Further research in this field has the potential to improve outcomes for individuals affected by these conditions and expand our knowledge of the relationship between viral infections and bone health.

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**ORCID ID:**
Yohana Haddish Mogos: 0009-0005-8249-217X

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