Inflammatory Sequelae After Chikungunya Virus Infection: Proposed Nutritional Treatment

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DOI 10.14200/jrm.2016.5.0103

ABSTRACT

Patients infected with chikungunya virus (CHIKV) exhibit specific characteristics, including high fever, rigors, headache, photophobia, petechial rash or maculopapular rash, and incapacitating joint pain. It is thought that the presence of CHIKV immunoglobulin M (IgM) and IgG antibodies play an important role in a new type of rheumatoid arthritis reported in 2009. It has been reported that 97% of patients with CHIKV infection complain of recurrent symptoms for 6 months. Fatigue was considered to be totally disabling in 4.6% of patients and very disabling in 42.8% of patients. Only 10% of patients considered their mood normal, whereas 37.8% felt demoralized and 43.9% considered their mood weakened. This article presents our review of the literature in which we looked for an effective nutritional approach for the treatment of CHIKV infection and its sequelae. It has been reported that the use of omega-3 fatty acids, intravenous vitamin C, bromelain, and curcumin plays an important role in decreasing the inflammatory response during an acute viral illness and other inflammatory processes, such as rheumatoid arthritis. Our general recommendation based on the current evidence, is that the use of omega-3 fatty acids, intravenous vitamin C, bromelain, and curcumin could be an effective treatment option for the inflammatory sequelae of CHIKV infection.

Keywords: Chikungunya; Omega-3 fatty acids; Vitamin C; Bromelain; Curcumin; Sequelae

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INTRODUCTION

Chikungunya fever, for which there is no cure or vaccine, is a viral infection. The chikungunya virus (CHIKV) is a member of the *Togaviridae* family and is part of the alphavirus genus.[1] It is an enveloped positive-strand RNA virus that has a 12-kb genome. CHIKV originated in West Africa, from where it colonized to other areas of Africa and eventually was introduced into Asia in 1960.[2] Infection of humans is mediated by *Aedes* spp. mosquitoes,[3] mainly *Aedes aegypti*, *Aedes albopictus*, and *Aedes polynesiensis*.[1] Infection with CHIKV results in a high fever, rigors, headache, photophobia, and a petechial or maculopapular rash. Additionally, many infected individuals present with severe, incapacitating joint pain. Classically, infected people adopt a characteristic walking position, the hallmark of the disease, from which it derives its name *chikungunya*, meaning "to walk bent over" in the Kimakonde language of Mozambique. Once a patient begins to recover from the acute phase of the infection, quality of life can be significantly affected by the inflammatory consequences of the infection.[4] It has been reported that relapses tend to occur in patients over 40 years of age and in those with other comorbidities, such as rheumatoid arthritis (RA) or traumatic illness.[5] High viral load levels during the acute stage of the infection have also been associated with the inflammatory consequences of the virus.[6] Real-time polymerase chain reaction data show that 105–1012 copies per milliliter of blood indicates strong viremia.

Symptoms persist for the first 90 days postinfection and consist primarily of malaise, joint pain, and inflammation of tendons, and these symptoms lead to patients becoming more dependent in their activities of daily living.[4] However, all the symptoms that have been associated with the rheumatic effects of CHIKV occur in the chronic stage of the infection.[7] The prominent symptoms reported include distal poly- or monoarthritis that is refractory to nonsteroidal anti-inflammatory drug (NSAID) treatment, tenosynovitis of the joints that is responsive to corticosteroids, and an increase in pain in previously injured tissues.[4]

It has been reported that 97% of patients infected with CHIKV complain of recurrent symptoms for 6 months and that these symptoms impact their energy and mood. Fatigue was considered totally disabling and very disabling in 4.6% and 42.8% of patients, respectively. Only 10% of patients considered their mood normal, whereas 37.8% felt demoralized and 43.9% considered their mood weakened.[8] In 2009, a new type of RA based on the presence of anti-CHIKV IgM and IgG antibodies was reported. Bouquillard and Combe[9] reported the development of symmetric polyarthritis in 21 patients older than 45 years of age over a period of 10 months.

Although CHIKV RNA has never been detected in the joints of patients in the chronic phase of the infection, it has been detected in the satellite cells 90 days postinfection.[10] In addition, macrophages have been shown to release key factors that mediate the inflammatory response during infection with alphaviruses.[11] In a patient who experienced symptoms consistent with CHIKV infection, specific autologous or microbial arthritogenic peptides secondary to the CHIKV infection were thought to possibly have been the cause of the chronic joint disease.[12] Interleukin (IL)-1, IL-6, and IL-8 are detected at high levels in the lymphocytes of infected patients, in addition elevated expression of the genes encoding for cytokines and chemokines involved in the pathophysiology of arthritis.[13,14]

Previous studies involving patients with RA suggest that neutrophilia induces an increase in IL-17, which results in the destruction of extracellular matrix, causing bone reabsorption and ultimately an increase in IL-6 production.[15] This supports the finding that patients with recurrent arthralgia post-CHIKV infection have increases in IL-6 and granulocyte-macrophage colony-stimulating factor versus patients who fully recover.[16] However, fully recovered patients have elevated levels of hepatocyte growth factor, which helps in cartilage repair. Additionally, patients had elevated levels of eotaxin, a type 2 cytokine that produces a local anti-inflammatory response.[17]

We propose a nutritional and botanical approach for the treatment of patients with inflammatory sequelae of CHIKV infection. There is evidence

supporting the use of intravenous omega-3 fatty acids, vitamin C, bromelain, and curcumin for the treatment of inflammatory diseases; therefore, they may be useful in the treatment of the inflammatory sequelae of chikungunya infection. The recommendations being made are based on the best preliminary data available, not on any double-blind clinical trials.

OMEGA-3 FATTY ACIDS

Omega-3 fatty acids, specifically eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have been shown to decrease neutrophil and monocyte chemotaxis.[18,19] Maximal inhibition occurs at a combined dose of at least 1.3 g of EPA and DHA.[20] In addition, EPA and DHA ingestion can decrease the adhesive interactions between endothelial cells and leukocytes when an inflammatory response is triggered.[21,22] Researchers in one study found that ingestion of 1.5 g of EPA and DHA daily resulted in diminished expression of intercellular adhesion molecule 1 (ICAM-1) on blood monocytes following *ex vivo* stimulation with interferon-γ.[23] Recently, researchers showed that supplementing with 1.8 g of EPA and DHA daily decreased the adhesive interaction between monocytes and endothelial cells in patients with peripheral vascular disease.[24] Other studies documented that EPA and DHA inhibit the production of IL-6 and IL-8 from immune cells when stimulated by endotoxins,[25,26] whereas fish oil has been shown to inhibit the production of tumor necrosis factor (TNF)-α in monocytes.[27] In patients with RA, dietary supplementation with omega-3 fatty acids results in a reduction in IL-1,[28] IL-1β,[29] and TNF-α[30] levels. NR1C3, or peroxisome proliferator activated receptor-γ, demonstrates anti-inflammatory activity.[31] This receptor has been shown to be activated by omega-3 fatty acids[32] and therefore causes a reduction in TNF-α and IL-6,[33] potentially resulting in a reduction in the inflammatory sequelae of CHIKV infection. In addition, omega-3 fatty acids were found to decrease the production of eicosanoids such as prostaglandin E_2 (PGE_2) from arachidonic acid.[34–36] Other studies conducted with healthy human volunteers showed decreases in PGE_2 and leukotriene B4 after subjects used fish oil supplements for a couple of weeks to months.[18,19,37] Researchers in a 3-month study involving healthy volunteers found that taking 1.35 g of EPA daily was insufficient to decrease PGE_2 production but that a daily intake of 2.7 g of EPA significantly decreased the production of PGE_2.[38] Therefore, the recommended dose of EPA should be greater than 1.35 g per day, up to 2.7 g of EPA daily, to reduce inflammation.[39]

VITAMIN C

Vitamin C has been shown to have an inhibitory effect on nuclear factor-κB,[40] a protein responsible for cytokine production. In 2012, in an investigation involving patients with cancer, researchers found that intravenous infusion of 50 g of vitamin C caused a reduction in the levels of the proinflammatory cytokines IL-2, TNF-α, and eotaxin.[41] Vitamin C has been widely used to prevent a variety of viral infections, including the common cold.[41–44] Recently, a confirmed case of CHIKV infection treated with high doses of intravenous vitamin C (100 g/day) was reported.[45] In that case, the patient showed improvement within 24 hours, with C-reactive protein (CRP) of 26.9 mg/L and 15.8 mg/L before and after treatment, respectively. That report supports the findings of other case studies in which researchers have found vitamin C to be an effective agent in the treatment of acute viral infections. The exact mechanism of action is still unclear; however, vitamin C (ascorbic acid) has been found to be an effective antiviral agent due to its ability to silence viral RNA and DNA.[43]

BROMELAIN

Another potential treatment for the inflammatory sequelae of CHIKV infection is the use of bromelain, an enzyme found in pineapple. This enzyme has been used in various autoimmune diseases,[46,47] such as RA,[48,49] and has been shown to be equally as effective as NSAIDs in the treatment of osteoarthritis (OA).[50,51] It has also been compared with other anti-inflammatory agents, such as dexamethasone.[52,53] On the basis of this previous research, we propose use of bromelain instead of

NSAIDs in the treatment of patients who are diagnosed with CHIKV infection. In 2008, bromelain demonstrated an ability to decrease the migration of neutrophils that were activated by IL-8 both *in vivo* and *in vitro*.[54] The researchers who reported that finding also proposed the proteolytic removal of receptor CD128 as a possible mechanism of action of bromelain. Bromelain's activity is measured in gelatin-digesting units (GDUs) or milk-clotting units (MCUs), with 1 GDU roughly equaling 1.5 MCUs. Bromelain should be taken on an empty stomach and is recommended at a dosage range of 500–1000 mg three times daily between meals, which provides 6000 GDU or 9000 MCU daily.

CURCUMIN

Curcumin is the active ingredient present in *Curcuma longa*, commonly known as the cooking spice turmeric. Recently, this spice has received special attention due to its anti-inflammatory properties. Many targets have been proposed for curcumin, including transcription factors, protein kinases, cytokines, cyclooxygenase (COX)-1 enzyme, and many other mediators of apoptosis, cell proliferation, and inflammation.[55] Curcumin has the ability to inhibit the COX-2 enzyme due to reduced expression of PGE_2[55]; however, this occurs when it is used in higher concentrations.[56–58] On the basis of previously reported data, it was determined that, at a concentration of 30 μmol/L, curcumin decreases the production of PGE_2 and COX-2/prostacyclin synthase-derived 6-keto-$PGF_1\alpha$.[59]

In 2011, curcumin was used in combination with methotrexate to treat arthritis in mice and also reduced the liver damage induced by this drug.[60] Researchers in a 3-month study used 200 mg of curcumin daily in patients with OA. Western Ontario and McMaster Universities Arthritis Index scores were reduced in 58% of patients, and patients reported more endurance in walking activities and a reduction in CRP from 168 to 11.3 mg/L.[61] In one study, patients were given 500 mg of curcumin, 50 mg of diclofenac, or a combination of curcumin and diclofenac.[62] Patients in the curcumin group had decreases in their American College of Rheumatology criteria for swelling and tenderness in their joints as well as better disease activity scores. Because curcumin is poorly absorbed, it should be taken with meals. To improve absorption, it is recommended that curcumin be paired with black pepper (piperine). Various forms of curcumin have been shown to have improved absorption, which include curcumin phytosome complexed with phosphatidylcholine, as seen in Meriva (Indena, Milan, Italy) or BCM-95 (Dolcas BioTech, LLC, NJ, USA); as a nanoparticle, as seen in Theracurmin (Natural Factors, Coquitlam, BC, Canada); and as water-soluble curcumin, such as polyvinyl pyrrolidone.

CONCLUSIONS

The described nutritional approach is appropriate for patients with active CHIKV infection as well as for patients with the inflammatory sequelae of CHIKV. CHIKV infection has been defined as a type of RA; therefore, treatment with curcumin, omega-3 fatty acids, bromelain, and vitamin C, which have demonstrated effectiveness in treating inflammatory diseases, can be used effectively and with fewer and less severe side effects in patients with CHIKV. While the data we have presented is compelling, randomized, controlled trials are needed to expand our knowledge of nutritional medicine and to determine whether such an approach offers greater benefit to patients when compared to traditional medical management.

On the basis of existing evidence, our general recommendations are as follows:

1. Omega-3 fatty acids molecularly distilled 1 g three times daily
2. Vitamin C (intravenous form) 50–75 g three times weekly for at least 2 weeks, followed by 1 g three times daily
3. Bromelain 1 g three times daily between meals
4. Curcumin 500 mg three times daily taken with meals

DISCLOSURE OF INTERESTS

The authors have nothing to disclose.

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