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Review

Possible benefits of micronutrient supplementation in the treatment and management of HIV infection and AIDS

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Recently, several reports have indicated that individuals living with HIV/AIDS undergo a condition of chronic oxidative stress with a resultant decline in nutritional antioxidants and other micronutrients. It has also been reported that these micronutrient deficiencies interfere with immune functions, weaken epithelial integrity, contribute to oxidative stress and enhance HIV disease progression. Reports from observational studies have led to an increasing interest in the possible benefits of micronutrient supplementation as a cost-effective strategy for improving oxidative and nutritional status. Micronutrient supplementation may also assist in the possible prevention of vertical transmission of HIV from mother to child especially in low-income countries where antiretroviral therapy and prophylactic drugs are not readily available. However, there are conflicting reports from other observational studies as to the usefulness or benefits of micronutrient supplementation in the treatment and management of HIV/AIDS. In this review we examine possible benefits of micronutrient supplementation in the treatment and management of HIV infection and AIDS.

Key words: Vitamins, antioxidants, micronutrients, supplementation, HIV infection, AIDS.

INTRODUCTION

In July 2008, UNAIDS reported that by December 2007, there were an estimated 33.0 million people globally living with HIV infection. It also stated that the number of cases of new HIV infections have decreased from 3.0 million in 2001 to 2.7 million in 2007. The report also showed that 2.0 million have died globally due to AIDS-related disease in 2007 compared with an estimated 1.7 million AIDS-related deaths in 2001. The report further states that although the percentage of people who are living with HIV appears to have stabilized, the overall number of people living with HIV infection has steadily increased as new HIV infections occur on a yearly basis. According to the UNAIDS report, Southern Africa continues to bear a disproportionate burden of HIV infection with 35% of HIV infection and 38% of AIDS-related deaths reported in Southern Africa in 2007. In total, Sub-Saharan Africa is reported to be home to 67% of all people living with HIV (UNAIDS, 2008).

The general question is whether micronutrient supplementation can play a beneficial role in reducing the burden of HIV infection, improve quality of life and contribute to the improvement of nutritional status of people living with HIV/AIDS.

The use of vitamins, minerals or other supplements is considered to be a popular complementary therapy by people living with chronic diseases such as HIV/AIDS and even by the general public. It has been reported that the UK population spends about US$800 million annually while their USA counterparts spend US$15.7 billion/year on supplements. It has also been observed that since the beginning of the HIV/AIDS epidemic, the use of vitamins/minerals and other nutritional supplements has been one of the methods adopted by people living with HIV/AIDS as a complementary therapy to improve their general health status and quality of life as well as possibly reverse or slow down HIV disease progression and increase their survival rate. Even with the availability of antiretroviral therapy (ART) micronutrient supplementation is still being viewed as an important and

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integral part of HIV and AIDS treatment (Nerad et al., 2003; Fawzi, 2003; Oguntibeju et al., 2003, 2006, 2008; Fawzi et al., 2004; Cunninggam-Rundles et al., 2005).

The micronutrient deficiencies are common in most HIV-infected people interfere with immune responses, weaken epithelial integrity and are linked to accelerated HIV disease progression (Baum et al., 1997; Ireton-Jones and Stiller, 1998; Cunninggam-Rundles et al., 2001; Dreyfuss and Fawzi, 2002; Nerad et al., 2003; Fawzi et al., 2004; Cunninggam-Rundles et al., 2005). Evidence from observational studies has renewed interest in the potential of micronutrient supplementation as a cost effective strategy for improving immune status, reducing HIV disease progression, improving nutritional status and possibly in reducing vertical transmission of HIV especially in low-income countries where antiretroviral therapy is not readily available. Micronutrient supplementation also may delay the onset of advanced disease and thus postpone the need for antiretroviral therapy, saving antiretroviral drugs for when they may be most needed and reducing drug-related adverse events and costs (Semba and Tang, 1999; Fawzi, 2003; Fawzi et al., 2004).

REASONS FOR MICRONUTRIENT SUPPLEMENTATION

People use supplements for various reasons. One such reason is the prevention of illness through nutritional strengthening of the immune system. In addition, supplemental micronutrients act as antioxidants that protect proteins, DNA and lipid damage by reactive oxygen species (Semba et al., 1993; Semba, 1997; Tang et al., 1997; Look et al., 1997; Wellinghausen et al., 2000; Lorenz et al., 2001; Lai et al., 2001; Piwoz, 2004; Fawzi et al., 2004). Another reason some people consume nutritional supplements is to counter the side-effects of certain medications. For example, protease inhibitors may increase the risk of cardiovascular disease and it is believed that vitamin C and folic acid may provide some protection from this effect by acting as antagonists to homocysteine (Baum et al., 1997). People living with HIV also utilize dietary supplements to reverse nutritional deficiencies that commonly occur in persons with HIV/AIDS, especially in developing countries with low social-economic status (Watson, 1994; Baum et al., 1995; Coutsoudis et al., 1997; Baum and Shor-Posner, 1998; Allard et al., 1998; Kanter et al., 1999; Piwoz and Preble, 2000; Piwoz, 2004).

IMPORTANCE OF NUTRITION TO HEALTH AND MEDICAL TREATMENT

For many years, adequate nutrition has been known to benefit people living with HIV/AIDS. Fenton stated that "Practitioners must be aware that good nutrition is not an 'alternative' therapy but a fundamental component of medical care" and that an individually-designed nutritional programme can boost immune function, increase the efficacy of other medical treatments, improve energy levels as well as enhance a general quality of life (Fenton, 1990). For example, a study in Africa found that the daily intake of vitamin B complex and multivitamins delayed the onset of AIDS and death in HIV-positive individuals (Fawzi et al., 2004). Other studies have shown that combined dietary supplementation with zinc, selenium and vitamins C, A, E, and B may increase AZT's antiviral effect while at the same time strengthen the immune system (Piwoz and Preble, 2000; Fawzi, 2003; Fawzi et al., 2004; Oguntibeju et al., 2006, 2008).

Conversely, malnutrition may contribute to the development of opportunistic infections and physical deterioration which can be the underlying cause of death in HIV-infected individuals (Babamento and kotler, 1997; WHO, 2003; Nerad et al., 2003; Piwoz, 2004). Cimoch (1999) reported on the primary role of nutrition in the treatment regimens of people living with HIV and explains that good nutrition improves the health status of people living with HIV, just as with any other infection, by providing essential nutrients that an active immune system requires in order to function efficiently. Various nutritional therapies are presently being evaluated in the USA and other countries and volunteer groups like the Treatment Alternative Research Project are advocating the undertaking of clinical trials of nutrient and other "alternative" and non-pharmaceutical treatments that could be of use in the treatment and management of HIV/AIDS.

RELATIONSHIP BETWEEN NUTRITION, IMMUNITY AND HIV INFECTION

The relationship between nutrition and HIV infection has been reported previously. HIV infection has been known to compromise the nutritional status of HIV-infected persons and a poor nutritional status has been shown to affect the progression of HIV infection (Allard et al., 1998; Lorenz et al, 2001; Jiamton et al., 2003; Piwoz, 2004). HIV infection could affect the nutritional status of an infected person in different ways: via a reduction in food intake, reduction in nutrient absorption, gastrointestinal and oral pathology, increasing the utilization and excretion of proteins and micronutrients (Roy et al., 1994; Watson, 1994; Piwoz and Preble, 2000).

It has been demonstrated that HIV infection increases the release of pro-oxidants, cytokines and ROS leading to increased utilization of antioxidant vitamins such as A, E, C, beta-carotene as well as microminerals such as iron, zinc, selenium, manganese and copper. This can result in an imbalance between pro-oxidants and antioxidants which may lead to increased oxidative stress which in turn may cause further damage to human cells, proteins and enzymes, thus accelerating HIV replication

and mortality of the patient (Tang et al., 1997; Friis and Michaelsen, 1998). Scientific reports support the view that vitamins and minerals are critical in reducing HIV disease progression and it has been shown that these micro-nutrients are required by the immune system and major organs to attack infectious pathogens (Tang et al., 1996; Chandra, 1997; Oguntibeju et al., 2003). Micronutrients and micronutrient supplementation have been shown to improve the effectiveness of the immune system and to reduce the severity and impact of opportunistic infections in people living with HIV/AIDS (Tang et al., 1997; Piwoz and Preble, 2000). In contrast, nutrient deficiencies are associated with immune dysfunction and accelerated progression to AIDS (Fawzi and Hunter, 1998; Macallan, 1999, Bijlsma, 2001). For instance, low levels of vitamin B_{12} and other micronutrients have been associated with a reduction in $CD4^+$ T-cell count in HIV-infected patients (Baum et al., 1995).

Recent studies have shown that nutritional deficiency begins early in the asymptomatic stages of the HIV infection and worsens over time and that nutrient deficiencies occur while $CD4^+$ T-cell counts are still in the preclinical range of 500-700 cells/mm^3. Also, it is claimed that nu-trient supplementation could restore immune function and may even boost $CD4^+$T-cell counts in people with early stages of HIV infection/disease. Even though there are reports which support the beneficial effects of nutrition and supplements on immune functions and other outcomes, there are health professionals who still ignore this area of patient health care. Current research findings support the need for resolution of nutrient deficiencies in order to achieve a full HIV management strategy (Baum et al., 1997; Baum and Shor-Posner, 1998).

MECHANISM OF ACTION OF ANTIOXIDANTS AND OXIDATIVE DAMAGE IN HIV INFECTION

Antioxidants are compounds that dispose, scavenge and suppress the formation of free radicals or oppose their actions. Free radicals, primarily the ROS, superoxide and hydroxyl radicals, which are highly reactive, with an unpaired electron in an atomic or molecular orbit, are generated under physiological conditions during aerobic metabolism (Roy et al., 1994; Semba, 1997; Look et al., 1997; Semba and Tang, 1999; Champe et al., 2005). Because free radicals are potentially toxic, they normally are inactivated or scavenged by antioxidants before they can damage lipids, proteins or nucleic acids.

Superoxide dismutase (SOD), catalase and glutathione peroxidase (GSH-Px) are the primary antioxidant en-zymes involved in the direct elimination of ROS whereas glutathione transferase, glucose-6-phosphate dehydro-genase (G6PD) and copper-binding ceruloplasmin are secondary antioxidant enzymes which assist in maintaining a steady concentration of glutathione and NADPH required for optimal functioning of the primary antioxidant enzymes (Graham et al., 1991; Kiremidjian-Schumacher et al., 1994; Champe et al., 2005). Antioxidant enzymes require micronutrients such as selenium, iron, copper, zinc and manganese as co-factors for optimal catalytic activity and to act as effective antioxidant defence me-chanisms. If homeostasis between the rate of formation of free radicals and the rate of neutralization of free radicals is not maintained, oxidative damage, known as oxidative stress occurs and further damages the already compromised immune system and consequently enhances HIV progression (Baum et al., 1995; Cunningham-rundles, 2001; Cunningham-rundles et al., 2005).

MECHANISM OF RECEPTOR-MEDIATED ENDOCYTOSIS AND THE ROLE OF ANTIOXIDANTS

Phagocytosis is the ingestion of micro-organisms and foreign bodies via the mechanism of receptor-mediated endocytosis by cells such as neutrophils and macro-phages. It is an essential body defence mechanism in bacterial and viral infections (Champe et al., 2005). The oxygen-dependent mechanisms include the myelopero-xidase (MPO) system and a system that generates oxygen-derived free radicals. An invading organism is recognized by the immune system and attacked by antibodies that bind it to a receptor on a phagocytic cell. Following the internalization of the organism within a membrane-bounded vesicle (the phagolysosome), NADPH oxidase located in the phagolysosome mem-brane converts molecular oxygen into superoxide which itself is converted spontaneously into hydrogen peroxide. In the presence of MPO, a lysosomal enzyme present in the phagolysosome, hydrogen peroxide and chloride ions are converted to hypochlorous acid which kills the invading organism. Any superoxide that escapes the phagolysosome is converted to hydrogen peroxide by superoxide dismutase (SOD); the hydrogen peroxide is neutralized by catalase or glutathione peroxidase. It should be noted that the activity of the enzymes NADPH oxidase and SOD depend on the availability of antioxi-dants as well as certain vitamins and minerals for proper functioning of the mechanism of the receptor-mediated endocytosis (Lorenz et al., 2001; Jiamton et al., 2003; Champe et al., 2005).

RESEARCH STUDIES ON MICRONUTRIENT SUPPLEMENTATION MULTI-VITAMINS

In 2004, Fawzi et al. recruited 1078 pregnant women infected with HIV in a double-blind, placebo-controlled trial in Dar es Salaam, Tanzania to study the effects of dietary supplementation with vitamin A (preformed vitamin A and beta carotene), multivitamins (vitamins B, C and E) or placebo on the progression of HIV disease, using survival models. The median follow-up with respect to survival was 71 months. The investigators found that women who randomly received multivitamin

supplementation were less likely to demonstrate progression to advanced stages of HIV disease, had better preservation of $CD4^+$T-cell counts and lower viral load and showed lower HIV-related morbidity and mortality rates than women who received a placebo. Vitamin A appeared to reduce the effects of multivitamins and when given alone, it (vitamin A) had some negative effects. The authors concluded that multivitamin supplements delayed the progression of HIV disease and provided an effective, low-cost means of delaying the initiation of antiretroviral therapy in HIV-infected women.

A cohort study also showed that daily multivitamin and mineral supplement intake reduced the risk of low $CD4^+$ T-cell counts and of HIV disease progression by 40 and 31% respectively (Abrams et al., 1993).

Vitamin C

Research has suggested that at higher intakes than the recommended daily allowance (RDA), vitamin C has a unique pharmacological function, displaying the potential to serve as an antioxidant under conditions of druginduced glutathione (GSH) deficiency or free radical toxicity. People living with HIV/AIDS have been shown to manifest striking GSH deficiencies and often exhibit symptoms of acute scurvy characterized by life-threatening weight loss, brittle bones and swollen glands (Kelly et al., 1999). It has been reported that GSH deficiency can result from changes in dietary vitamin C intake. Volunteers who were fed controlled diets containing vitamin C at lower levels than the RDA, showed de-creased concentrations of GSH in plasma (Abrams et al., 1993). Administration of a vitamin C rich diet (250 mg/dl) in the same study resulted in restoration of plasma GSH concentration. It has been shown that at high concen-trations, vitamin C can act as a direct scavenger of free radicals as well as being able to convert oxidized forms of non-enzymatic scavengers (tocopherol and GSH disul-phide) to their reduced states (Beisel, 1990; Tang et al., 1996., 1996). Continual ROS production in HIV-infected persons may cause the biological system to consume antioxidants (free radical scavengers) at an increased rate which may lead to de-pletion of vital antioxidants such as vitamin C in the body.

Because antioxidant depletion and a chronic scorbutic state are associated with HIV/AIDS patients, metabolic functions of vitamin C are potentially relevant to the con-trol and management of such conditions in HIV-infected persons. In a cohort study conducted by Tang et al. (1993), 25% of the volunteers with a high intake of ascorbic acid (715 mg/day) in food and supplements combined, showed a significant progressing to AIDS. It has been reported that ascorbic acid is associated with increased survival rate however, no relationship has been found between ascorbic acid from supplement alone and survival. Oguntibeju et al. (2006) reported that HIV-positive/AIDS patients supplemented for three months on an ascorbic acid-containing supplement-experienced a reduced viral load and improved haematological parameters such as mean cell haemoglobin (MCH) and mean cell haemoglobin concentration (MCHC). Unfor-tunately, no increase in $CD4^+$Tcell counts was observed. Oguntibeju et al. (2008) reported that in a population with a limited access to antiretroviral therapy, the findings that nutrient supplementation maintained the body mass index (BMI) as well as lean body mass (LBM) indicates a contributing role of nutritional supplements on the quality of life and the general well-being of HIV positive patients. However, the authors pointed out that the sole use of nutritional supplements is not a substitute for antiretro-viral therapy and that antiretroviral therapy is the better approach for treating HIV/AIDS patients.

Abrams et al. (1993) published results from two-six year epidemiological studies, one of which was a study of 296 men in a prospective study of dietary intake and AIDS in homosexual men. The authors observed that a higher intake of micronutrients was associated with a higher $CD4^+$T-cell count; the daily use of multivitamins was associated with a reduced risk of AIDS and a significantly reduced risk of a low $CD4^+$T-cell count. Progression to AIDS was reported to be slower with a higher intake of vitamin C. In another study, individuals with the highest quartile of vitamin C intake had significantly more AIDS-free time than those with lower vitamin C intake (Tang et al., 1993).

Vitamin E

Vitamin E is necessary for the proper functioning of the immune system. Vitamin E increases humoral and cell-mediated immune responses, antibody production, pha-gocytic and lymphocytic responses and exhibit resistance to viral and infectious diseases (Watson, 1994; Tang et al., 1997; Allard et al., 1998). The oxidative stress cre-ated by HIV infection and related opportunistic infections increase the utilization of antioxidant vitamin E, possibly leading to deficiency. Vitamin E deficiency could in turn further weaken the immune system, increasing the susceptibility of people with HIV/AIDS to opportunistic infections (Chandra, 1997). High baseline serum vitamin E concentrations were associated with decreased HIV progression after taking into account HIV-related symptoms, $CD4^+$ T-cell count, age and other confounding variables (Tang et al., 1997). In this study, individuals with serum vitamin E concentrations greater than 23.5 mmol/l took 34% longer to develop AIDS than those with low serum vitamin E concentrations, suggesting a healthy status on HIV disease progression.

Allard et al. ((1998) reported that three months of supplementation with vitamin E (800 IU) and vitamin C (1000 mg) significantly reduced the oxidative stress and HIV viral load in HIV-positive/AIDS patients. A study done in Zambia among AIDS patients suffering from persistent diarrhoea found that vitamin E deficiency at baseline

predicted mortality in the following month (Kelly et al., 1999).

B vitamins

The intake of thiamine, riboflavin, niacin and vitamin B_{12} were positively associated with improved $CD4^+$T-cell counts and inversely associated with HIV disease progression in male patients (Abrams et al., 1993). Vitamin B_{12} deficiency is relatively uncommon in healthy populations but low serum vitamin B_{12} concentrations are common among asymptomatic HIV-infected persons (Tang and Smit, 1998). Low B_{12} concentrations are associated with neurological and immunologica abnormalities such as neuropathy, myelopathy, impaired cognition, reduced $CD4^+$ T-cell count, increased bone marrow toxicity and increased mortality (Tang and Smit, 1998). A 9-month study conducted among homosexual and bise-xual men with HIV in the USA found that men with low serum vitamin B_{12} concentrations at baseline had significantly shorter AIDS-free survival times than men with adequate B_{12} concentrations (Tang et al., 1997). A retrospective case-control analysis among HIV-infected patients in South Africa reported that patients who supplemented their diets with B vitamins increased their survival time by 120 weeks (Kanter et al., 1999).

Beta carotene

In a study carried out by Abrams et al. (1993), the dietary intake of beta carotene was not associated with immunologic and clinical progression of HIV-infected subjects. On the other hand, Tang et al. (1996) reported that increased beta carotene intake improved survival rate in HIV-positive subjects. A randomized study of 21 HIV-positive subjects showed that a 4-week of daily beta carotene supplementation resulted in significant increases in total white blood cell count, and $CD4^+$T-cell count while supplementation with placebo decreased these counts (Coodley et al., 1996). In another study of 52 HIV-positive subjects, supplementation with beta carotene (60 mg taken daily), improved overall oxidative status although $CD4^+$T-cell count were not affected (Constans et al., 1996).

Vitamin A

The relationship between vitamin A and HIV disease progression has been studied the most extensively. However, results have not been consistent and in certain cases the results have been contradictory. Abrams et al. (1993) reported that vitamin A intake was positively associated with the $CD4^+$T-cell count as well as a slower progression to AIDS and Tang et al. (1993) reported that moderate vitamin A intake was associated with a reduced risk of disease progression and death. However both studies reported that a high intake of vitamin A did not protect against HIV disease progression in HIV-infected persons. Consistent with these reports, Baum et al. (1995) reported that a decrease in serum vitamin A concentration was related to a decrease in $CD4^+$T-cell count and others have reported that conducted among HIV-positive drug-user men in the USA, low serum vitamin A concentrations can significantly increase the risk of death (Semba et al., 1993, 1994).

In contrast to these reports, low serum vitamin A concentrations did not predict mortality among a cohort of HIV-infected drug users over time (Baum et al., 1997). Also, randomized trials have not demonstrated that vitamin A supplementation slows HIV disease progression among adults. An analysis of a subsample of women from a clinical trial conducted in South Africa on vertical HIV transmission, found that vitamin A and beta carotene supplementation during the third trimester of pregnancy has no effect on viral load and that vitamin A supplementation did not slow down the immunologic progression of HIV disease (Coutsoudis et al., 1997). In a large randomized placebo-controlled clinical trial among HIV-positive pregnant women which was conducted in Dar es Salaam, Tanzania, it was reported that daily vitamin A supplementation had no significant effect on $CD4^+$T-$CD8^+$, $CD3^+$ cells or viral load; these investigators advised HIV-infected persons to avoid taking megadoses of vitamin A (Fawzi et al., 2004).

SELENIUM AND IMMUNE FUNCTION

Selenium deficiency has been associated with impaired function of the immune system (Cunninghan-Rundles, 2001, 2005). Selenium supplementation in individuals who are not overtly selenium deficient appears to stimulate the immune response. In two small studies, healthy and immuno-compromised individuals, supplemented with 200 mcg/day of selenium as sodium selenite for eight weeks, exhibited an enhanced immune cell response to foreign antigens compared to the responses of subjects given a placebo (Roy et al., 1994; Kiremidjian-Schumacher et al., 1994, 2000). A considerable amount of basic research also indicates that selenium plays a role in regulating the expression of cell signaling molecules such as cytokines, which orchestrate the immune response (Baum et al., 1997; Kiremidjian-Schumacher et al., 2000).

SELENIUM AND VIRAL INFECTION

Selenium deficiency appears to enhance the virulence or progression of some viral infections and that the increased oxidative stress resulting from selenium deficiency may induce mutations or changes in the expression of some viral genes. For example, when selenium-deficient mice were inoculated with a relatively harmless

strain of Coxsackie's virus, mutations occurred in the viral genome that resulted in a more virulent form of the virus, causing an inflammation of the heart muscle known as myocarditis. Once mutated, the mutated virus also caused myocarditis in mice that were not selenium deficient. A study in mice that lack the cellular (classical) glutathione peroxidase enzyme (GPx-1 knockout mice) demonstrated that cellular glutathione peroxidase provides protection against myocarditis resulting from mutations in the genome of a previously benign virus. Selenium deficiency results in decreased activity of glutathione peroxidase with a resultant increase in oxidative damage and the likelihood of mutation in the viral genome. Coxsackie virus has been isolated from the blood of some sufferers of Keshan's disease, suggesting that it may be a cofactor in the development of the cardiomyopathy associated with selenium deficiency in humans (Kiremidjian-Schumacher et al., 2000).

SELENIUM AND HIV INFECTION

It has been reported that there is an interaction between selenium and the human immunodeficiency virus (HIV) that causes acquired immunodeficiency syndrome (AIDS) Zhao et al., 2000). Decreasing plasma selenium concentrations in HIV-infected individuals are sensitive markers of disease progression and severity, even before malnutrition becomes a factor (Fawzi, 2003). Low levels of plasma selenium have also been associated with a significantly increased risk of death from HIV infection (Kiremidjian-Schumacher et al., 2000). It has been observed that adequate selenium nutritional status may increase resistance to HIV infection by enhancing the function of important immune system cells ($CD4^+$ T-cells) and modifying the production of intracellular messengers known as cytokines (Mocchegiani and Muccizoli, 2000; Nerad et al., 2000; Lai, 2001). In HIV infection, increased oxidative stress appears to favor viral replication, possibly by activating specific transcription pathways (Kiremidjian-Schumacher et al., 2000). As an integral component of glutathione peroxidase and thioredoxin reductase, selenium plays an important role in decreasing oxidative stress in HIV-infected cells possibly suppressing the rate of HIV replication. Recent research indicates that HIV may be capable of incorporating host selenium into viral selenoproteins that have glutathione-peroxidase activity (Zhang et al., 1999; Zhao et al., 2000). Though the results of the study will require further clarification, the authors suggest that both the human immune system and the activity of the virus are affected by selenium and nutritional status.

Only a few trials of selenium supplementation in HIV-infected individuals have been conducted. Two uncontrolled trials of selenium supplementation (one using 400 mcg/day of selenium-enriched yeast and the other using 80 mcg/day of sodium selenite plus 25 mg/day of vitamin C) reported subjective improvement but did not demonstrate any improvement in biological parameters that reflect to AIDS progression (Constans et al., 1996). Another clinical study followed 15 HIV-infected patients supplemented with 100 mcg/day of sodium selenite and 22 non-supplemented patients for one year and found that selenium supplemented patients exhibited evidence of decreased oxidative stress and significant reductions in HIV progression (Roy et al., 1994). However, there were no differences in $CD4^+$ T-cell count or mortality between the supplemented and non-supplemented patients. A randomized control trial in 186 HIV-positive men and women found that 2 years of selenium supplementation at 200 mcg per day, significantly decreased hospitalization rates (Kiremidjian-Schumacher et al., 2000). In a randomized, double-blind placebo-controlled trial in 174 HIV-1-positive individuals, selenium supplementation (200 mcg/day of selenium-enriched yeast) for nine months was associated with increased serum selenium concentrations, increased $CD4^+$ T cell counts, and reduction in HIV replication (Lai et al., 2001).

ZINC AND HIV INFECTION

Because adequate intake of zinc is essential for maintaining immune system function, HIV-infected individuals are particularly susceptible to the effects of zinc deficiency (Graham et al., 1991; Baum et al., 1995; Mochengiani and Muzzioli, 2000). Decreased serum zinc concentrations have been associated with advanced disease and increased mortality in HIV patients (Mochengiani and Muzzioli, 2000). In one of the few zinc supplementation studies conducted in AIDS patients, daily dietary supplementation with 45 mg/day of zinc for one month, decreased the incidence of opportunistic infections when compared to the effects of a placebo (Mochengiani and Muzzioli, 2000).

However, the HIV virus also requires zinc, and excessive zinc intake may stimulate the progression of HIV infection. In observational studies of HIV-infected men, increased zinc intake was associated with more rapid disease progression and any intake of zinc supplements was associated with poorer survival (Graham et al., 1991; Abrams et al., 1993; Baum et al., 1995). These contradictory results indicate that further research is necessary to determine optimal zinc intakes for HIV-infected individuals.

AUTOIMMUNITY AND HIV INFECTION

There is increasing evidence that autoimmune disease due to HIV infection may be treated with antioxidants and other micronutrients that protect cell membranes and reduce the inflammatory response by the body due to HIV infection (for example., glutathione, coenzyme Q-10, antioxidant vitamins, selenium, zinc). According to Lands, deficits in any of the nutrients essential to maintain

immune competence, can contribute to immune dysfunction and possibly cause autoimmune conditions (Lands, 1992). At the Linus Pauling Institute in Palo Alto, California, researchers have shown that vitamin C (a water-soluble antioxidant), may block HIV infection of cultured cells although the mechanism of this effect remains unknown (Higdon, 2006). Vitamin C is distributed widely throughout the body and may increase the effectiveness of compounds such as N-acetylcysteine which in turn helps to replenish glutathione. Lands reported that researchers in the USA demonstrated that, *in vitro* NAC, slows down HIV replication by inhibiting viral transcription (production of messenger RNA, the template for protein production) (Lands, 1992).

In addition to antioxidants, it may be very important to address other factors that can contribute to auto-immune conditions in HIV infection such as food and chemical hypersensitivities. Appropriate discovery of such sensitivities via tests such as the serum ELISA/ACT test, followed by elimination of the foods or other items to which sensitivity is found, may help counter the possible auto-immune outcome of HIV/AIDS (Gross and Newberne, 1980; Beach, 1989; Dedich, 1990; Beisel, 1990).

MICRONUTRIENT SUPPLEMENTATION AND POTENTIAL EFFECTS OF MEGA-DOSING

For people who intend or desire to take supplemental vitamins and minerals in addition to a balanced diet, a multivitamin which provides at least 100% of the U.S. Recommended Daily Allowance (RDA) is preferable over individual vitamins because of the importance of nutrient balance, lower cost and lower risk of toxicity. However, individual vitamins can be used as supplements when needed. Multivitamins also are preferred because single-nutrient deficiencies are less common than multi-nutrient deficiencies in individuals with immune dysfunction due to HIV-induced malnutrition (Nerad et al., 2003; Fawzi et al., 2004). Therefore, the daily intake of a single, good multivitamin may be more cost-effective, safe, and logical than a supplementation with a variety of individual nutrients (Beisel, 1982). Furthermore, some vitamins (e.g vitamin C) are water-soluble and are excreted in the urine when super-saturation due to mega-dosing occurs.

However, despite the high cost and time involved, mega-dosing may perhaps be effective for some people in certain cases. Most studies of high micronutrient intake in humans and animals have shown mega-dosing to be safe, and have demonstrated improved immune function when supplements are given at two to five times the RDA (Brighthorpe, 1987; Fawzi et al., 2004). However, the dangers of mega-dosing in vitamin supplementation should not be ignored and caution should be exercised since toxic effects are possible when vitamins are used incorrectly or when a mega-dose is taken, as has been observed in the case of vitamin A or zinc. Fawzi et al. (2004) reported that mega-dosing of vitamin A is not beneficial to people living with HIV/AIDS. Routine blood tests should therefore be used to monitor concentrations and ensure that supplementation does not produce vitamins or mineral toxicity (Brighthorpe, 1987).

CONCLUSION AND RECOMMENDATIONS

This review has shown that HIV/AIDS and nutrition are interrelated and that HIV infection affects nutrition through the development of symptomatic and AIDS. Nutrition intervention such as micronutrient supplementation is beneficial for people living with HIV/AIDS, although mega-doses of vitamin A or zinc could have adverse effects in HIV-infected persons. However, more studies are needed on the specific micronutrient requirements of HIV-positive individuals. Therefore, nutritional counseling is important.

Nutritional counseling has been shown to be effective and to influence health outcomes in HIV infection. It has been reported that when dietary counseling is combined with nutritional supplements, it adds additional value and facilitates access to adequate dietary intake. It should however also provide information on the importance of adequate and balanced diets and therefore should include recipes for preparing meals. There also is a need to emphasize the importance of optimizing and maintaining nutritional status. It is also necessary to emphasize to patients the importance of early treatment of opportunistic infections because infections increase the need for nutrients, impair nutrient absorption and reduce dietary intake.

Health professionals should provide information on alternative therapies cautiously and should provide guidelines for home-based assessment of basic anthropometric indices such as body weight. Nutritional intervention should begin early in patients diagnosed with HIV infection or AIDS, evaluation of nutritional status should be conducted on a regular basis and nutritional supplementation should form an important and integral part of the clinical management of infected patients. Nutritional intervention can strengthen the immune system, replace lost micronutrients and reduce the severity or impact of opportunistic infections.

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