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ANTIOXIDANTS AND ALCOHOL IN THE PROGRESSION OF ACQUIRED IMMUNODEFICIENCY SYNDROME

by

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ABSTRACT

Wasting syndrome in acquired immunodeficiency syndrome (AIDS) appears to play a role in decline of immune function. Along with poor appetite, HIV infected individuals seem to have a tendency to be heavy alcohol drinkers which may be immunosuppressive and cause malnutrition. Altered macronutrient metabolism visibly contributes to wasting; however, micronutrient deficiencies also appear to play a role. Micronutrient deficiency has also been known to decrease immune function. As part of their role as antioxidants, β-carotene, vitamin C, vitamin E, and selenium may be helpful in altering cell production and response to cytokines and other secretions. This may decrease viral replication and prevent wasting syndrome.

INTRODUCTION

In 1996, the prevalence of acquired immunodeficiency syndrome (AIDS) in the United States was 235,470 (1). This is a 11% increase from 1995 when the number of people with AIDS was 173,560. However, in the same time period the mortality rate decreased 23% from 50,140 to 38,780 due to the advances made in HIV therapies. In addition to more effective medication, diet and nutrition has also been found to play an important role in the mortality of AIDS patients. Since weight loss, malnutrition and wasting are characteristic traits of human immunodeficiency virus (HIV) and AIDS, it was estimated that approximately 80% of patients with HIV/AIDS died malnourished in the recent past (2). While many patients still suffer from malnourishment and wasting, proper nutritional intervention has been found to help in treating and restoring immune function as well as preventing disease progression and weight loss (3). The effects of single
nutrients on the immune system and progression of AIDS have been of particular interest lately. This paper will focus on the effects of alcohol and antioxidants in the progression of AIDS.

**REVIEW OF IMMUNE RESPONSE**

The body consists of two types of immune responses to antigens (foreign material in the body): humoral and cell-mediated (4). The humoral response consists of B-lymphocytes which can be divided into memory and plasma cells (4). Memory B-cells remember previous antigens so that the body can respond to the same type of antigens quicker than at the time of original exposure. After exposure to a familiar antigen, memory B-cells transform into plasma B-cells, which produce antibodies that interact with the antigen (4).

Cell-mediated response is the body's main defense against antigens (4). It consists of T-lymphocytes, natural killer cells, and monocytes. T-lymphocytes also have memory cells, but effector cells to carry out the main action against the antigen (4). Helper, suppressor, and cytotoxic lymphocytes are those that are termed as effector cells. Helper T-lymphocytes (CD4) signal memory B-cells to transform into plasma B-cells (4). Conversely, suppressor T-lymphocytes signal B-cells to stop transformation (4). When antibodies from B-cells identify antigens, cytotoxic T-lymphocytes (CD8) and natural killer cells are then able to destroy the cells that are infected by the antigen (4).

Monocytes are the other type of cell-mediated response. Through conversion into macrophages, this type of cell becomes extremely phagocytic and is able to process the antigen so that it is recognized by T and B-lymphocytes (4). Another function of monocytes is to produce cytokines and prostaglandins to help regulate the immune responses in the body (4). (However, monocytes are not the only type of immune cell to produce these substances.)
HIV INFECTION PROCESS

HIV is a Ribonucleic Acid (RNA) retrovirus (3). When the virus enters a new host, it is covered with cell membranes, antibodies, and/or complement from the infected donor (5). This enables the host’s immune system to recognize it as foreign to the body and treat it like an antigen complex (5). Through an interaction with helper T lymphocytes (CD4+) and macrophages, the retrovirus binds to the surface receptors of these cells and is internalized (5,6). Once inside, the retrovirus is uncoated and the viral RNA is transcribed to Deoxyribonucleic Acid (DNA), using an enzyme called reverse transcriptase (3,6). The proviral DNA is then incorporated into the host’s chromosomal DNA through use of a viral enzyme, endonuclease (6). This is how the host chromosomal DNA remains for the life of the cell (6). The virus, however, continues to transcribe RNA into DNA, thus causing an accumulation of proviral DNA to build up in the cytoplasm (6).

Even with the proviral DNA incorporated into the cell’s chromosomal DNA, the integrity of the cell is maintained for as long as the viral DNA remains latent (6). Antigens, coinfecting viruses, and cytokines can activate the viral DNA. When this happens, the DNA is transcribed into messenger RNA (mRNA) (6). This is then translated into viral proteins which are responsible for virion RNA replication (6). When virion RNA is produced, the virion RNA and a viral protein envelope then bud off from the cell to infect other cells (6).

The HIV infection targets the host’s CD4+ cells and progressively depletes them (7). Since these cells are a major part of the body’s defenses against infection, HIV infection eventually leads to immunodeficiency, secondary infections, and neoplasms (7). Other immune cells (e.g. B-lymphocytes, monocytes, and macrophages) are also affected by HIV (6).

The amount of time varies for each individual from HIV infection to development of AIDS
It usually takes around 7-11 years for the infection to progress to AIDS (8). AIDS is diagnosed when an individual is HIV seropositive and has wasting syndrome (or another life threatening clinical condition that can unequivocally be linked to HIV-induced immunosuppression) (7,8). Also, an HIV-infected individual with a CD4 cell count of less than 200 cu/mm, regardless of clinical status are diagnosed as having full blown AIDS (9).

**WASTING SYNDROME**

Wasting syndrome is defined by the Center for Disease Control (CDC) as involuntary weight loss of greater than or equal to 10% of original body weight in one month (7). The etiologies of wasting syndrome is decreased food intake, malabsorption, and cachexia (10). Cachexia associated with HIV/AIDS hypothesized to be related to an increase in the production of cytokines (especially tumor necrosis factor [TNF]) with resultant hypermetabolism (10).

One researcher noted that the majority (68%) of AIDS patients in their study were hypermetabolic (8). Additionally, some have noticed that when AIDS patients become infected with opportunistic infections, a decreased food intake often did not lead to a compensatory decrease in metabolic rate, thus theoretically causing weight loss and wasting (8). Others have failed to find this paradox, and increased amounts of cytokines were not always found to correlate with hypermetabolism (8).

While the exact mechanism for the relationship between cytokine production, metabolic disturbances, viral burden, and weight loss are not completely understood, several hypotheses exist: endocrine abnormalities and altered macronutrient metabolism (8). Endocrine abnormalities that are currently under study include: 1) alteration in thyroid hormone triiodothyronine levels leading to hypermetabolism and 2) decreased levels of testosterone and dehydroepiandrosterone (DHEA) in men associated with cytokine dysregulation, and loss of nutrients and weight (8).
However, these areas are still controversial, and further studies need to be done in these areas.

Altered macronutrient metabolism appears to be due to cytokine dysregulation. In murine (adult mice) AIDS, the TNF is found to increase hepatic lipogenesis and hepatic release of very low density lipoproteins (VLDLs) (8). TNF also seems to inhibit adipocyte lipoprotein lipase and enhance adipocyte lipolysis (8). Thus, fatty acids are mobilized and shuttled to the liver where they are packed into VLDLs. The VLDLs are then released into the bloodstream and circulate throughout the body. However, the VLDLs can not be broken down to release the fat; therefore the fat is not stored or used for energy but remains circulating the bloodstream in the VLDL form (8,11). Other cytokines have been suggested to also interact with lipoproteins and result in a decrease clearance of triglycerides from the body (11). This inability to use fat as an energy source especially in the presence of malnutrition results in the body’s use of lean tissue mass (proteolysis) in order to supply the body with needed energy (11). There seems to also be futile cycling of glucose (8). However, it is not as common as fat cycling.

TNF may also enhance viral replication through a positive feedback mechanism (11). When HIV is taken into a macrophage, the cell stimulates the production of TNF. The TNF then may increase viral replication in that cell as well as other mononuclear phagocytes. Thus, as more cells are infected with HIV, they in turn increase the amount of TNF produced in the body.

ANTIOXIDANTS ANDS AIDS

In addition to altered macronutrient metabolism, micronutrient deficiencies also play a role in the development of wasting syndrome and AIDS (10). Micronutrient deficiencies can decrease immune function (12). Antioxidants (β-carotene, vitamin C, vitamin E, and selenium) seem to be of particular interest in the latest research.

It has been hypothesized that humans infected with HIV experience chronic oxidative
stress which may play a role in stimulating HIV replication (13). Allard et al. (14) did a study on lipid peroxidation and plasma antioxidant micronutrient levels in patients with HIV infection. Forty-nine nonsmoking HIV seropositive subjects without any active opportunistic infections and 15 age-matched seronegative controls were provided with a preliminary diet that consisted of a polyunsaturated to saturated fat ratio of 0.3:1 for two weeks. Blood samples were then collected from each participant to be evaluated for plasma carotenes, plasma α and γ tocopherol, vitamin C, selenium, zinc, and lipid peroxides. HIV-positive subjects had significantly lower levels of vitamin C, α and γ tocopherol, β-carotene, and selenium than controls. Additionally, lipid peroxidation was significantly higher in the HIV-positive group.

Kotler (15) also suggested that reactive oxygen species accentuate viral replication. Oxidants are believed to further contribute to the development of HIV into AIDS by enhancing the loss of CD4 cells by apoptosis (programmed cells death). Antioxidants were hypothesized to have a role in the treatment of viral diseases from alleviating disease symptoms and decreasing the long term effects of chronic oxidative stress.

While it appears that HIV-positive patients experience chronic oxidative stress and have lower plasma levels of antioxidants, the question that remains is whether supplementation with antioxidants is beneficial. Delmas-Beauvieux et al. (16) studied the effect of selenium and β-carotene supplementation in HIV-infected patients. Thirty-seven HIV-infected subjects (18 receiving a placebo, 14 receiving oral selenium supplements of 100 µg/day, 13 receiving oral β-carotene supplements of 60 mg/day) were given treatment of a placebo, selenium supplement, or β-carotene supplement for 12 months to determine the effect on enzyme activity and selenium concentrations in the body. At the end of the study, those supplemented with selenium had a significantly higher selenium concentration and activity of one enzyme (glutathione peroxidase)
compared to baseline levels and other treatments. The placebo group decreased in all areas and β-carotene supplementation decreased in all areas except for enzyme activity of glutathione peroxidase. However, the amount of increased activity was not significant.

In another study (17), 72 HIV-positive patients were randomly assigned to two groups. The first received 60 mg of β-carotene orally 3 times daily, and the other group received a matched placebo. Additional to the treatment supplement, all participants took a multivitamin. Baseline values for T-cells subsets, natural killer cells, HIV p24 antigen, serum β-carotene levels, and a complete blood count were obtained from each participant at the beginning of the study and were retaken at 1 month and at 3 months into the study. The results showed no significant difference in blood values except for serum β-carotene concentrations between treatment regimens. The researchers hypothesized that the lack of difference could have been due to the fact that both groups received a multivitamin. However, a similar studies (18) done on β-carotene supplementation have failed to show any major changes in the total lymphocyte counts and showed significant increases in T-cells for 3 months of supplementation. However, this effect diminished after 4 months of treatment, even thought the subjects remained on the β-carotene supplements.

Further studies on selenium also showed a beneficial effect. Hori et al. (19) evaluated the effectiveness of selenium supplementation in vitro on HIV replication. Supplementation of selenium occurred three days before exposure of T-lymphocyte and monocyte cells to TNF. The results showed that selenium partially helped to suppress induction of HIV-1 replication in both chronically infected T-cells and monocytes. However, in acute infection of HIV in both types of cells exposed to TNF, selenium only helped to suppress replication in monocytes and not in T-lymphocytes. Interestingly enough, selenium had no effect on HIV replication in monocytes and
T-lymphocytes when the cells were not exposed to TNF. This suggests that selenium has a protective effect against TNF-induced HIV replication. Selenium is also beneficial because it increases activity in cellular antioxidant selenoproteins: glutathione peroxidase, and thioredoxin reductase.

Wang et al. (20) did a study on female mice infected with a retrovirus functionally similar to human AIDS to determine the effect of vitamin E supplementation on cytokine production. Retrovirus infection occurred the day before vitamin E supplementation was begun. Supplementation occurred at 150 IU/day, 1500 IU/day, and 4500 IU/day for 10 weeks. Results showed that concentrations of hepatic and serum levels of vitamin E were significantly decreased by the retrovirus infection. Vitamin E supplementation at all levels significantly increased hepatic and serum levels. However, supplementation with 1500 IU/day and 4500 IU/day did not further increase either hepatic or serum levels significantly over 150 IU/day. In cytokine production, vitamin E supplementation significantly restored production of the cytokines, interleukin-2 (IL-2) and interferon-\(\gamma\) (IFN-\(\gamma\)), that are normally suppressed in murine AIDS. While no significant increase was seen between doses of vitamin in the production of IFN-\(\gamma\), IL-2 production correlated with the increase in vitamin E supplementation. In interleukin-6 (IL-6), interleukin-10, and TNF levels, vitamin E supplementation significantly reduced secretion which is normally found to increase in AIDS. For IL-6 and IL-10, supplementation over 150 IU/day showed no further decrease that was statistically significant. TNF, however, showed further reduction in 1500 IU/day and 4500 IU/day over that of 150 IU/day. Thus, vitamin E supplementation seems to normalize body vitamin E levels and cytokine production in murine AIDS. This potentially would help to prevent wasting syndrome which may be related (at least in part) to dysregulation of cytokine production as was mentioned previously in this paper.
Another study of vitamin E supplementation, evaluated whether vitamin E helped to normalize IgE antibody levels in HIV patients. Shor-Posner et al. (21) compared IgE levels in nine HIV-positive men with vitamin E deficiency with 16 HIV-positive men without vitamin E deficiency, and 20 HIV-negative men. The results showed a dramatic increase in IgE levels: 308 +/-112 IU/ml, 118 +/- 41 IU/ ml, and 59.5 +/- 15.7 IU/ml, respectively. This study also found a strong relationship between IgE levels and CD8 cell counts. It is hypothesized that vitamin E induces a decrease in immunosuppressor prostaglandins and other lipid peroxidation products to normalize IgE levels in the body and improve immune response.

While β-carotene supplementation did not seem to not have much of an effect on immune function, vitamin E and selenium supplementation appear to have a beneficial effect on the immune system through antioxidant functions and normalizing cytokine and other body secretion regulation. No studies were found on the effect of vitamin C supplementation in AIDS. The mechanism for their beneficial effect may be related to their antioxidant function. By protecting cells from oxidative damage, they may also reduce production of cytokines and other secretions that enhance viral replication. This is turn would result lower the amount of cells that would be infected and destroyed by HIV. Additionally, by altering the body’s response to cytokines, vitamin E and selenium may be helpful in the preventing wasting syndrome which is also known to decrease immune function.

**ALCOHOL AND AIDS**

Alcohol is also a hot topic in AIDS research, since heavy alcohol consumption seems to be a tendency of those individuals infected with HIV. To begin heavy alcohol consumption is common among intravenous drug users and has been associated with sexual inhibition; thus placing those people at high risk of being exposed to HIV infection (8,22). Bagasra et al. (22) did
a study on the effect of ethanol on HIV infection. Twelve healthy, seronegative subjects abstained from alcohol for 10 days prior to the study. Nine were injected with 500 mg/kg of ethanol, and three were injected with saline. Blood was drawn from each subject at 30 minutes before injection and 30 minutes, 1 hour, 2 hours, 24 hours, 48 hours, 72 hours, and 120 hours after injection. Each subject's blood was then infected with HIV in vitro. As assessed by mean HIV-1 p24 antigen levels, infusion of ethanol was associated with an increase in the replication of HIV.

Previous studies done by the same group of researchers also showed that alcohol consumption was associated with a decline in the functions of helper and suppressor T lymphocytes (22). Other studies have shown that in people who consumed a large amount of alcohol progression from HIV infection to AIDS took only a few months compared with the 7-11 years that was mentioned before (8). Another study was done involving HIV infected subjects and uninfected controls who were heavy alcohol drinkers (8). When the HIV infected subjects quit drinking, they had an increase of 41% in CD4+ cells while uninfected controls only had a 15% increase.

In studies done on murine AIDS, alcohol acted as a cofactor for enhancement of the progression of AIDS by worsening cytokine disturbances, decreasing immune function, and further suppressing resistance to pathogens common in AIDS patients (8). HIV infection, as well as alcohol, both separately caused antioxidant loss from tissues resulting in further damage to DNA and loss of lymphocyte function (8). This suggests that not only does alcohol have a direct effect of immune depression, but also an indirect effect of malnutrition through decreased consumption of other nutrient dense foods and malabsorption. Both effects enhance the progression of AIDS (8).
CONCLUSIONS

From looking at these studies, it would appear that alcohol consumption has a depressive effect on the immune system which enhances progression of HIV to AIDS. Also, a indirect effect of malnutrition may contribute to wasting syndrome, and therefore enhancing the progression of AIDS. Supplementation of vitamin E and selenium appears to be helpful in preventing cytokine dysregulation to decrease viral replication and prevent wasting syndrome. However, the effect of β-carotene supplementation is not as clear. Clearly, more research is needed in these areas to substantiate what has been found.
REFERENCES


