Murine AIDS studies define antioxidant deficiency mechanisms

Dear Sir:

The exciting study of Allard et al (1) confirms apparently unrecognized studies of murine AIDS showing increased lipid peroxidation occurring concomitantly with reduced concentrations of antioxidant vitamins in tissue (2-4). Replacement of vitamin E reduced lipid peroxidation and immune dysfunction (2), which slowed cancer development (3), whereas vitamin A supplementation prolonged survival (5), in murine AIDS. However, ethanol consumption increased oxidation, accentuated immune dysfunction, stimulated cancer, and accelerated death during retrovirus infection (3, 6). Animal model studies (2, 3) have already answered a key question in Allard et al's study; will supplementation with antioxidant vitamins reduce oxidative stress?

The authors queried, what are "the mechanisms underlying the increased oxidative stress in the HIV population?" Retrovirus oxidation increased production of T helper 2 cell cytokines by a subset of cells, highly activated by retroviral antigens (2, 4). In murine AIDS, suppression of these cytokines by injection with a T cell receptor peptide prevented excessive oxidation, loss of vitamin E, and retrovirus-induced immune dysfunction (4) while maintaining resistance to an opportunistic pathogen (7).

Murine retroviral oxidation, loss of antioxidant vitamins, and cytokine dysregulation have been prevented both by vitamin E (2) and antioxidant hormone (dehydroepiandrosterone) supplementation (8) and immunologically by direct suppression of the excessive cytokine secretion of T helper 2 cells with T cell receptor peptides (4, 7). Such knowledge from the murine AIDS model, supported by the current study in human AIDS (1), should be applied to human AIDS treatment (9). Over-the-counter antioxidant hormone or vitamin supplementation appears safe and efficacious in murine AIDS and in uninfected humans. Therefore, supplements of antioxidant hormones or vitamins should now be used to overcome antioxidant deficiencies in HIV-infected persons (9). This should help to prevent the loss of disease resistance and the resulting cytokine dysregulation due to retrovirus-induced antioxidant deficiencies, while we await confirmation of the benefits of such supplements in HIV-infected patients from clinical trials (10).

Ronald Ross Watson

Arizona Prevention Center
1501 North Campbell Avenue
University of Arizona
School of Medicine
Tucson, AZ 84724

REFERENCES

Reply to RR Watson

Dear Sir:

We thank Watson for his interesting letter. We knew that both animal (1, 2) and in vitro experiments (3) have shown that antioxidant vitamins reduce oxidative stress, improve immune function, and decrease HIV replication. These experiments were the basis for our study investigating oxidative stress and antioxidant defense status in HIV-infected humans (4). The key question of whether supplementation with antioxidant vitamins will reduce oxidative stress that Watson refers to concerns humans rather than animal subjects and relates not only to...
oxidative stress but also to HIV replication and disease progression. Although animal studies are exciting, results from these studies cannot be used as claims of efficacy in the treatment of human diseases unless proper clinical trials are performed. For example, vitamin E may slow cancer development in murine AIDS (5), but in human smokers (6), another oxidatively stressed population with antioxidant deficiencies, supplementation with vitamin E and β-carotene actually increased risk for lung cancer. What about the HIV population? Observational studies (7, 8) suggest that over-the-counter multivitamin and antioxidant vitamin supplements may have some benefits and slow the progression to AIDS. On the basis of our study (4), I agree with Watson that such supplements may be used in an attempt to overcome antioxidant deficiencies. However, it is not yet proven that these supplements given to humans infected with HIV will result in the same efficacy as reported in in vitro or animal studies. So far, few trials have addressed this issue. In HIV-infected patients, a trial investigating the effect of β-carotene supplementation on immune function was negative (9) and another with selenium and β-carotene produced mixed results (10).

Therefore, from our point of view, although antioxidant supplementation has been proven to be of benefit in animal models, the data on supplementation in humans are unfortunately lacking. We hope to be able to remedy this in the near future; we have now documented increased oxidative stress and antioxidant micronutrient deficiencies in humans infected with HIV. As for "the mechanisms underlying the increased oxidative stress in the HIV population," we agree with Watson that it is likely these are related mostly to activated polymorphonuclear leukocytes and cytokine production, as mentioned in the introduction of our article (4).

Johane P Allard

The Toronto Hospital, General Division
200 Elizabeth Street, EN-217A
Toronto, Ontario M5G 2C4
Canada

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Bioimpedance: 50 kHz parallel reactance and the prediction of body cell mass

Dear Sir:

Several important comments need to be made concerning the paper by Kotler et al (1). Although a rhetorical case was made for body cell mass (BCM) predicted by 50-kHz parallel reactance (Xp), no theoretical basis was provided. Kotler et al stated that a major uncertainty in the theory underlying bioelectrical impedance analysis is whether the body's ionic circuit is arranged as a series or parallel circuit. We can find no rigorous study in the literature supporting this statement or any single-frequency (SF) prediction of cell volume. It was suggested that the improved prediction of total body potassium (TBK) by Xp compared with series reactance (Xs) was proof that Xp is superior for predicting BCM. Impedance measured at any SF can be interpreted as a series or parallel circuit, with both resulting in 2 final elements, resistance (R) and reactance (X). The problem is that biological tissue consists of >2 elements (2, 3). A 3-element model, consisting of resistance extracellular water (Rc) in parallel with a series cell membrane capacitance (Cm) and resistance intracellular water (Ri), has been used since 1925 to interpret impedance measurements on individual biological cells (2). Cole added an important fourth term to the model (exponent α) in 1940 to represent the effect of the infinite number of series Cm and Ri values (cells) in a cell suspension (tissue) (3). The improved correlation in predicting TBK-BCM with Xp compared with Xs is meaningless because Xs is not used for anything and neither Xp nor Xs has any scientific basis.

It should be noted that the Xp equation has R in it. The correlation and SEE values for the predicted BCM by Xp were only 0.04 and 1.1% better, respectively, than when series R alone was used (Kotler et al's Table 5). The same R was also used to predict total body water (TBW). Lukaski (4), who is now a proponent of an Xp-predicted BCM, previously promoted X as a measure of extracellular water (ECW). Confusingly, this was dismissed several years later by the same authors in Kotler et al's paper because X was contributing virtually nothing to the prediction (5). Resistance predicts ECW, intracellular water (ICW), and TBW with...