Figure 2. Estimated survival curves using landmark of diagnosis of AIDS. Cox regression analysis was used to estimate survival probability over time for patient with 105 CD4 cells/mm³ (median), hematocrit of 39% (median), high functional status, and no herpetic episodes and who was not receiving Pneumocystis prophylaxis prior to landmark. ACV, acyclovir.

References

Inflammation in Human Immunodeficiency Virus Type 1 Infection as a Cause of Decreased Plasma Retinol

To the Editor—Recently, Semba et al. [1] reported an association between plasma retinol concentrations <1.05 μmol/L and mortality among human immunodeficiency virus (HIV)–positive patients who died of infectious diseases with or without AIDS. The authors suggested that a reduced plasma retinol concentration (<1.05 μmol/L) is a functional indicator of vitamin A deficiency and inferred that vitamin A intake should be increased by supplementation to reduce mortality in HIV-positive patients with infections.

We believe that vitamin A deficiency may have been overestimated in this study for two reasons. First, the cutoff value for plasma retinol (<1.05 μmol/L) may be too high to correctly estimate the presence of vitamin A deficiency in this HIV-positive population and, second, it is possible that inflammation-induced changes in retinol transport, rather than vitamin A deficiency, may have been a cause of low plasma retinol.

References

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The cutoff value used by Semba et al. [1] to interpret their data originated from the National Health and Nutrition Examination Survey (NHANES) [2], in which age-specific distributions were determined for plasma total retinol (retinol plus retinyl esters) in the healthy US population. A plasma vitamin A value <1.05 μmol/L in adults was interpreted as indicating that “vitamin A status may improve with increased consumption of vitamin A; some individuals may exhibit impairment of function” [2]. However, no validation studies have been done to confirm the association of plasma vitamin A in this range with an impaired biologic function of vitamin A. Semba et al. [1] measured plasma retinol (vitamin A alcohol), which is expected to be somewhat lower than the sum of retinol and its esters as measured by NHANES [2]. We note that in a study that used dark adaptation as a functional indicator of vitamin A status, decreased dark adaptation was observed only when the concentration of plasma retinol-binding protein (RBP) was <0.95 μmol/L (20 μg/mL) [3]. Assuming ~80% saturation of RBP with retinol, the corresponding plasma retinol concentration is ~0.8 μmol/L. Thus, a plasma retinol concentration of 1.05 μmol/L may not be low enough to predict functional impairment due to vitamin A deficiency, especially in a small population of HIV-positive injection drug users.

Of greater concern is the interpretation of the cause of low plasma retinol. We believe that the inflammatory response may be a confounding factor, especially in HIV-positive patients dying of infectious diseases. The dysregulation of cytokines has been documented in HIV-1 infection, especially the oversecretion of proinflammatory cytokines [4] and references therein), which are correlated with a reduction in CD4 T cells and progression to AIDS [5, 6]. These cytokines regulate the synthesis of acute-phase proteins in the liver, among which RBP is a negative acute-phase protein [7].

Recently, we showed that plasma retinol is reduced by 30%–40% in vitamin A–sufficient rats during endotoxin-induced inflammation [8]. This reduction in retinol was associated with decreases in RBP in plasma and liver; moreover, the mRNA for RBP was significantly reduced in the liver of endotoxin-treated rats [8]. These findings strongly suggest that RBP synthesis is decreased during inflammation such that less retinol is mobilized from plasma, and plasma retinol concentration is depressed. It is plausible that this mechanism also operates in HIV-positive patients, especially those with secondary infections. A recent cross-sectional study reported that 49% of AIDS patients had plasma retinol concentrations <0.15 μmol/L, compared with 2.1% in the NHANES population; however, the vitamin A intake among AIDS patients was adequate or well above the recommended daily allowance [9].

An effect of inflammation has also been suggested. Semba et al. [1] found a strong association between reduced plasma retinol and low hemoglobin concentrations, which was interpreted as an effect of vitamin A deficiency on iron metabolism. However, experiments with marginally vitamin A–deficient rats have shown only a slight reduction in hemoglobin concentration, and studies in pregnant women have demonstrated that only one-third of the hemoglobin concentration is restored by vitamin A supplementation alone [10] and references therein). Alternatively, the reduction in hemoglobin may be caused by an increased secretion of interleukin-6 [11] and may represent a response to inflammation.

Dupon et al. [12] reported lipid overload (mostly vitamin A esters) of perisinusoidal cells in the livers of AIDS patients. The overload was not associated with hypervitaminosis A and suggested an impaired secretion of vitamin A from the liver as a possible mechanism for the accumulation of vitamin A.

In conclusion, we believe that before inferring that vitamin A supplementation may improve plasma retinol concentrations and the clinical status of HIV-positive patients, it is important to scrutinize the cutoff value used to interpret data from studies such as that of Semba et al. [1] and, more important, to rule out other causes of hyporetinemia, such as infection and inflammation, which may adversely affect the plasma transport of retinol.

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References