When does hyporetinolemia mean vitamin A deficiency?\textsuperscript{1–3}

Charles B Stephensen

Serum retinol, which is bound to retinol binding protein (RBP), has at least 2 roles. One role (created by nutritionists) is to serve as an indicator of vitamin A status. Another role is to serve as the transport form of vitamin A from liver stores to peripheral tissues. Although most nutritionists would agree that the former role of serum retinol can be transiently compromised during the acute phase response, convincing evidence that the latter role is significantly compromised under the same circumstances is lacking. The authors of 2 studies—one involving women with night blindness (1) and the other involving children with night blindness or Bitot spots (2)—raise, but do not answer, the question of whether the low serum retinol concentrations seen during the acute phase response cause clinical manifestations of vitamin A deficiency (eg, night blindness).

Serum retinol concentrations decrease transiently during the acute phase response to infection and trauma for several reasons, including decreased release of retinol-RBP from the liver (3). Thus, serum retinol concentrations typically rebound during resolution of the acute phase response as retinol is again released from the liver. This phenomenon can complicate the use of serum retinol as an indicator of vitamin A status because by status, nutritionists typically mean the amount of vitamin A stored in the liver (4). Whereas infection or trauma may lead to loss of vitamin A from body stores during severe infections (5), transient decreases in serum retinol occur during mild episodes of infection and trauma as well and thus are clearly not directly related to decreases in liver vitamin A stores in such cases. These transient decreases impair the assessment of nutritional status when they decrease serum retinol concentrations to the extent that subjects may be misclassified as having less than adequate liver vitamin A stores when, in fact, their stores are adequate.

Persons with an active acute phase response may be identified by measuring serum concentrations of positive acute phase proteins, such as C-reactive protein (CRP) and α\textsubscript{1}-acid glycoprotein (AGP), which increase during the acute phase response (6). Such markers can be used to identify subjects with low serum retinol who may be misclassified as vitamin A deficient because of the acute phase response, a remedy that has been suggested to adjust measurements of other micronutrients as well (7). The concentrations of these acute phase proteins typically have a strong, negative correlation with serum retinol during the acute phase response. Semba et al (2) and Christian et al (1) found that such negative correlations are also found in subjects with clinical vitamin A deficiency, confirming that decreases in serum retinol induced by the acute phase response occur across a wide spectrum of vitamin A status. These findings are not unexpected.

In addition, Christian et al (1) found that the odds ratio for recent episodes of infection was greater in pregnant women with night blindness than it was in matched control subjects without night blindness. Semba et al (2) also found that children with xerophthalmia were more likely to have elevated AGP concentrations (as an indicator of recent infection) than were matched control subjects. Viewed from one perspective, these finding do no more than confirm that clinical vitamin A deficiency is often preceded by infection, the presumption being that infection somehow was associated with and probably contributed to the decrease in body vitamin A stores that result in night blindness and the corneal manifestations of xerophthalmia. However, these authors assert that a subject with diminished (but not depleted) liver vitamin A stores will already have a low serum retinol concentration. The additional, transient decrease caused by the acute phase response, they suggest, may be sufficient to critically decrease retinal vitamin A stores and thus induce clinical signs of deficiency (night blindness) that would not have occurred if infection had not intervened to decrease transport from the liver to the retina. This hypothesis is plausible but remains to be proven.

In this context, it is worth noting that naturally occurring mutations in the human RBP gene can result in extremely low serum retinol concentrations, night blindness, and retinal dystrophy but little else that is consistent with clinical vitamin A deficiency (8). RBP-knockout mice, which have similarly low serum retinol concentrations, appear to be largely healthy with only mild retinal alterations (9). These findings in humans and mice can also be viewed from 2 perspectives: 1) serum retinol does not matter because the clinical consequences of such low serum retinol concentrations are so mild, or 2) retinal function is the most sensitive physiologic indicator of impaired transport of vitamin A from the liver to peripheral tissues. (Other potentially sensitive indicators of vitamin A status, such as immune function, have not yet been examined in these RBP-deficient humans and mice.) This latter perspective suggests that if

\textsuperscript{1}From the US Department of Agriculture Western Human Nutrition Research Center, Davis, CA, and the Nutrition Department, University of California, Davis.

\textsuperscript{2}Supported by intramural funds from the US Department of Agriculture, Agricultural Research Service, Western Human Nutrition Research Center.

\textsuperscript{3}Address reprint requests to CB Stephensen, Nutrition Department, 3243 Meyer Hall, 1 Shields Avenue, University of California, Davis, CA 95616. E-mail: cstephensen@ucdavis.edu.

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the transient decreases in serum retinol that occur during the acute phase response are detrimental to the function of any tissue, the retina would be it. This possibility should be addressed with currently available techniques to further our understanding of the causes and consequences of vitamin A deficiency.

One final point seems appropriate, although it is not addressed by the 2 studies in question (1, 2). Even if transient decreases in serum retinol do have adverse consequences, might they not also have some unknown benefit, as proved to be the case with transient decreases in serum iron during acute infection (10)? (I know of no such benefits and have none to propose.) Also, even if such transient decreases do have adverse effects and no benefits, might there be arguments against intervening immediately to increase serum retinol concentrations during the acute phase response? We have learned that intervening with high-dose vitamin A supplements in children during acute infections who do not have clinical manifestations of vitamin A deficiency does not always produce benefits and may have some unexpected adverse consequences (11). Intervening is not always desirable and this should be kept in mind. In other words, hyporetinolemia induced by the acute phase response is not equivalent to vitamin A deficiency and thus does not merit a therapeutic intervention in the absence of clinical evidence (or a strong clinical suspicion) of vitamin A deficiency or persistence of biochemical evidence of vitamin A deficiency (4) after resolution of the acute phase response.

REFERENCES


