Letter to the Editor

Low Protein Diets and Blood Coagulation

Dear Dr. Visek:

I am writing to comment on the paper entitled “Low dietary protein impairs blood coagulation in BHE/cdb rats” by Chang et al. (1997). The BHE/cdb rat is a nonobese animal model of noninsulin-dependent diabetes mellitus that develops diabetes as it ages (Berdanier 1991).

These authors compared the effect of feeding a 50:50 mixture of lactalbumin and casein at 8 g/100 g of diet with one containing the same mixture at 38 g/100 g of diet to BHE/cdb rats. After 4 weeks they observed that certain indices of blood coagulation (bleeding time, clotting time, prothrombin time, activated partial thromboplastin time and Factor VII activity) were abnormal in the rats fed the low protein diet. Since the abnormalities observed are consistent with a vitamin K deficiency, I looked further into the conditions of their experiments.

I was surprised to note that the vitamin supplement which these investigators used was the AIN-76 mixture which provides only 50 mg of menadione per kilogram of diet as a source of vitamin K. It is known that menadione (a vitamin K precursor) must be alkylated to form menaquinone-4 in order to generate vitamin K activity (Dialameh et al. 1970), and that the overall conversion rate from isotopic studies varies from 1–5% (Dialameh et al. 1971). In addition, they found that the activity of the alkylating enzyme for menadione was 7 times more active in chick liver microsomes than in rat liver microsomes. The inadequacy of 50 μg/kg of menadione to prevent hemorrhage in rats fed diets low in protein or devoid of casein was reported shortly after the issuance of the AIN-76 report. (Bieri 1979, Roebuck et al. 1979).

It appears that the reason why many investigators employing experimental diets fashioned after the AIN-76 recommendation did not encounter defects in coagulation was that they used casein at 200 g/kg in their diets. Matschiner and Doisy (1965) reported that “vitamin-free” casein contains the equivalent of 600 μg of phylloquinone per kilogram. If true, this would provide 120 μg/kg in the usual purified diet, more than sufficient to meet the rats requirement for vitamin K (Kindberg and Suttle 1989). On this basis, in the studies of Chang et al. (1997), the low protein diet (80 g/kg) of which half was casein would provide only 24 μg of phylloquinone per kilogram of diet. In addition the 50 μg of menadione would provide at most the equivalent of only 10 μg of phylloquinone to bring the total of 34 μg phylloquinone/kg. The fats used in this study are also low in phylloquinone and did not contribute significantly to the vitamin K level.

In the most recent AIN recommendation on the formulation of purified diets (Reeves et al. 1993) menadione was replaced by phylloquinone at 15 times the AIN-76 level which represents an increase of about 75 times in biological activity. Although the BHE/cdb rat may have a slightly different system for converting menadione to menaquinone-4, it is unlikely that any genetic difference accounts for the defect in coagulation.

Robert E. Olson
Department of Pediatrics
University of South Florida
Tampa, FL 33606

LITERATURE CITED


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