

ALPHA-TOCOPHEROL AND CARCINOGENESIS

**MOHAMMED TARIQ AFTAB, ASIF BIN REHMAN
AND ZAFER SAFED SAIFY***

*Department of Pharmacology, *Department of Pharmaceutical Chemistry
Faculty of Pharmacy, University of Karachi, Karachi-75270, Pakistan*

Low serum alpha-tocopherol in cancer patients has been determined by a number of workers. However the reason of this deficiency can not be established as yet. We have tried to relate this deficiency to the hyperactivity of immune system of such patients. This relation can be supported indirectly by a number of studies conducted on the effect of different factors on serum alpha-tocopherol.

A number of workers have already determined low levels of alpha-tocopherol in cancer patients (Salonen et al., 1985 & Longnecker et al., 19--). However, the key mechanism leading to this deficiency is still not clear. In our view this is a result of the immune reaction which is developed in patients in response of the presence of tumour-specific and tumour-associated antigens. Presence of such reaction in cancer patients, is supported by a number of studies as detailed below:

- i) Iioachim (Ioachim, 1976) presented histologic examination of certain tumours in man, which had a heavy mononuclear infiltrate (lymphocytes, macrophages, plasma cells) in and about the tumour, particularly in certain carcinomas of the lung, testis and breast, malignant melanomas, and Hodgkin's disease.
- ii) Everson and Cole (everson et al., 1966) reported 130 instances of spontaneous regression of metastatic malignant tumours, half of them including chloriocarcinomas, hypernephromas, neuroblastomas, and malignant melanomas, for which immune responses were suspected.
- iii) Burnet (Burnet, 1970) brought forward the concept of immunologic surveillance against tumours, which is based upon these reactions. Although this concept had to face challenges, but it was firmly supported by numerous studies (Hersh, 1975).

The possible relationship of alpha-tocopherol to the immune system of the body is well established. The role of fat soluble vitamins in relation to immune mechanism of the body has been reported in a number of studies.

- i) Relatively high levels of dietary vitamin A in animals were found to be associated with the enhanced antibody production after antigen exposure, mitigation of the immunosuppressive effects of cortisol, enhancement of macrophage function (9) and delay in the onset of chemically induced tumours (10).

- ii) Nutritional deficiency of vitamin A in human leads to depress function of 'T' and 'B' lymphocytes, macrophages and neutrophils (9).
- iii) Deshazo and colleagues (11) showed the involvement of monocyte derived toxic oxygen mutabilities in lymphocyte dysfunction of Hodgkin's disease. They also showed augmentation of lymphocyte proliferation with the addition of catalase or alpha-tocopherol in the culture system.
- iv) Combined administration of vitamin E and C resulted in significantly better clinical improvement in patients with chloasma and pigmented contact dermatitis, an allergic manifestation (12). Similarly, vitamin E is found to improve immune system of patients (13).
- v) In acquired Immune Deficiency Syndrome (AIDS), the cell membrane distortion of the T-4 cells protein receptor for genetically related macrophage factor (GRF) is one of the possible effects of HIV virus on T-cells. The integrity of this specific T-cell receptor takes on profound significance due to its relationship to soluble antigen. Alpha-tocopherol has been shown to assist in the maintenance of cell membrane structure (14).
- vi) Vitamin E supplementation is found to suppress prostaglandin E₂ synthesis to enhance immune response of aged mice (15). Similarly this compound prevents a decline of natural killer cells activity under conditions where free radical formation by activated macrophages and polymorphonuclear leucocytes may be enhanced (16).

It appears as the immune reaction is set up due to presence of malignant cells in the body (Ioachim, 1976, Everson et al., 1966 & Burnet, 1970) which induces a feedback stimulus as a result of deliberate use of immune components. An enhanced demand of alpha-tocopherol is natural in such body environment, because of its close association to the body immune network (11-16). This seems to be the most important factor, in reducing the serum alpha-tocopherol levels in cancer patients. This is further supported by the reports in which low levels of certain vitamins are found in those diseases in which there is an excessive use of immune components. These vitamins are those vitamins, which play important roles in *body* immune system. For example:

- i) Low levels of ascorbic acid have been noted in the blood of patients with rheumatoid arthritis (17).
- ii) Vitamin A deficiency in animals produced enhanced susceptibility to respiratory infection, to cancer induction by chemical carcinogens and to decrease macrophage function (Vitale, 1979b).

- iii) Remarkable success of antioxidant treatment (Selenomethionine and vitamin E) was noted in the treatment of atopic eczema and asthma (Ahlrot-Westerlund et al., 1988).

A study done by Shaklar et al. (1990) provides the most direct evidence for the preventive role of alpha-tocopherol in development of carcinoma, through immune response. In their experiment, they tried to develop epidermoid carcinomas, in hamster buccal pouch by 7,12-dimethyl-benz(a) anthracene. They found that all those animals demonstrated gross tumour that had no alpha-tocopherol treatment, but no animal had the lesion, which received alpha-tocopherol during tumour induction. On microscopic study, they saw small foci of dysplasia and adjacent connective tissue infiltration of macrophages and lymphocytes in these animals who were treated by alpha-tocopherol. This provided a direct evidence for the hypothesis that alpha-tocopherol prevent the development of carcinoma by destroying early dysplastic lesions by an enhanced immune response.

Another factor which also seems to play an adjuvant role with alpha-tocopherol depletion due to immune reaction, is the tendency of malignant cells to concentrate certain vitamins, which are found to be low in cancer patients. supported by the following two reports.

- i) In first report, epidermoid carcinomas of the oral cavity and oropharynx from six patients were examined for the presence and amount of cellular retinol and cellular retinoic acid binding proteins. In all cases adjacent, grossly normal tissue was similarly examined. In these cases these proteins were found to be significantly higher in tumour tissue compared to adjacent tissue (Ong et al., 1982).
- ii) In second report, lipid extracts of Novikoff ascites hepatoma cells are found to contain considerably more vitamin E, than the extract of normal rat liver (Burton et al., 1983).

So, the tendency of malignant cells to pick significantly higher amount of alpha-tocopherol from serum takes part in the depletion of this compound in the body pool.

The role of patient's nutritional status in creating alpha-tocopherol deficiency requires to be emphasized now. Charpiot and his colleagues (1989) presented a study, in which they tried to link the levels of vitamin A and E to those plasma protein carriers like retinol binding protein with polyps and in patients who have digestive malignancies. They concluded that the reduction of retinol binding protein and prealbumin in these patients is due to protein deficiency. They suggested that decreased serum levels of vitamins A and E observed in digestive cancers are a consequence of this nutritional deficiency. This is true in digestive cancers due to obstruction in digestive passages or/and disbalanced digestive secretions or/and lack of healthy and satisfactory absorption

surface. But this is not true in other cancers. A study conducted by Brennan (1981) on nutritional and metabolic components of 55 tumour bearing patients, shows that although whole-body protein catabolism was significantly high but no change was found in whole body protein turnover and synthesis in 50 patients. An indirect evidence is also found by the ability of tumour necrosis factor to reproduce the metabolic abnormalities associated with malignancy which in doses that cause fever can result in accelerated whole body protein turn-over (Shike et al., 1989). The most important support in this respect, is provided by the study conducted by Shike and colleagues (1984) who found normal total serum proteins and serum albumin levels in patients with small cell lung cancer, who were suffering from malnutrition.

The momentum for the concept of diet as a possible etiologic factor comes from the basic carcinogenesis studies and population studies. The research conducted in this regard explores natural and synthetic substances, precisely finalized and measured, that demonstrate the potential to prevent, half or reverse carcinogenesis. Special attention is given to B-carotene, retinol and related synthetic retinoids, ascorbic acids and alpha-tocopherol.

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