Interrelationship of Micronutrients: Antagonism and Synergism

Tripathy S.¹, Dhaduk J. J.² and Kapadiya S.³
¹Research Scholar, ²Professor, ³Senior Research Assistant
Department of Food Science and Nutrition,
ASPEE College of Home Science and Nutrition
Sardarkrushinagar Dantiwada Agricultural University, Sardarkrushinagar-385506
*Corresponding Author E-mail: sucharattripathy1994@gmail.com
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ABSTRACT
Vitamins and minerals are considered as micronutrients for body but they play vital role in different body functions. These minerals and vitamins interact with each other’s either synergistically to increase each other’s activity or antagonistically to decrease their effectiveness in body. Major vitamin antagonisms include antagonism between vitamin A and D, vitamin C and vitamin K, vitamin K and some antibiotics, vitamin C and vitamin B₁₂, Fe, Co etc. Some of the important synergism between micronutrients includes thiamine, riboflavin, pantothenic acid, vitamin D, B₁₂, E. So during diet formulation these factors should be taken care to avoid any disorder.

Key words: Antagonism, mineral, synergism, vitamin

INTRODUCTION
In human body system, every nutrient has a specific role either directly on the body or through interfering with the function of other nutrients. These interrelationships among different nutrients either may be advantageous or may lead to deficiency of each other. A loss of this vital balance, particularly among different trace vitamins may lead to subclinical deficiencies or decreased bioavailability leading to different deficiency diseases.

Chemically vitamins are amines which are very much essential for maintenance of vital body function. They are present in small amounts in food. They are involved in the absorption and utilization of the major nutrients like proteins; fats and carbohydrates. Vitamins also have synergistic and antagonistic relationships. Vitamins are involved in several body functions such as they act as coenzymes and are involved synergistically in many enzymatic reactions. They can also protect against deficiencies of other vitamins.

Vitamin Antagonisms
An anti-vitamin is a substance which makes the vitamin unavailable or ineffective within the body. Specifically these substances block the action of some vitamins. Sometimes, the antagonism may not be direct but indirectly they may increase the requirements of target vitamins because of their excessive intake.
Vitamin A and D are mutually antagonistic to each other. Vitamin A reduces the toxic effects of vitamin D. Vitamin A enhances the absorption or retention potassium and phosphorus. It has been reported that vitamin B₁ can have an antagonistic action against vitamin B₁₂. The antagonistic relationship between vitamin C and vitamin B₁₂ is an indirect one. Vitamin C neither directly affects B₁₂, nor destroys this vitamin. Vitamin C enhances iron absorption. Increased amount of iron in body leads to deficiency of cobalt, which is an integral part of vitamin B₁₂. This is however a rare occurrence and may affect only a small segment of the population who may suffer from iron overload disorders.

**Vitamin A antagonists**

Blood-thinning medications and other drugs, including aspirin, phenobarbital, arsenicals and dicumarol (a drug used medically to retard blood clotting) destroy vitamin A in the body. Vitamin A is also depleted when nitrosamines are formed in the stomach from the union of nitrites with secondary amines and when the mucous membranes of our respiratory passages are exposed to air pollutants such as carbon monoxide, ozone, sulphur dioxide, nitrogen dioxide, lead, hydrocarbons, etc.

**Vitamin K antagonists**

The amount of vitamin K needed by humans is very small and a deficiency is highly unlikely because this vitamin is in a wide variety of commonly available plant foods and again it is synthesized by bacteria in the intestinal tract. However, antibiotic therapy (penicillin, streptomycin, tetracycline, chloromycin, terramycin, etc) suppresses bacterial growth and consequently, the synthesis of vitamin K. Other vitamin K antagonists include the drugs dicumarol and hydrocoumarol, which are used by medical people to relieve thrombosis (abnormal formation of blood clots in the blood vessels). As the chemical structure of these antihistamines is similar to that of vitamin K, they act as anticoagulants by interfering with the synthesis of pro-thrombin and the other natural clotting factors. Large doses of vitamin A can also inhibit the absorption of vitamin K.

**Vitamin C and vitamin E interactions**

Vitamin C and vitamin E are both antioxidants and protect against reactive oxygen species. These substances are of parallel interest as water-soluble vitamin C regenerates lipid soluble vitamin E in an outside the cell of the organism. There is much evidence indicating that vitamins C and vitamin E may also have a physiologically relevant interaction.

In guinea pigs, vitamin C deficiency led to reduced levels of vitamin E and administration of oxidized frying oil, large doses of vitamin C increased the level of vitamin E in the liver, kidney, spleen, and lungs. In inherently scorbutic rats, vitamin C deficiency led to reduced vitamin E levels in the liver, kidney, and heart. In normal rats, vitamin C supplementation increased plasma vitamin E level. Contradicting to this Hruba et al. reported that vitamin C deficiency did not affect the plasma vitamin E level in guinea pigs. The excessive doses of vitamin C may reduce plasma vitamin E levels.

The estrogen in oral contraceptives is also an antagonist of vitamin E. Vitamin C reacts with several alien substances in the bloodstream. All drugs and pollutants can be considered as vitamin C antagonists. Some of the foremost vitamin C antagonists include ammonium chloride, sibisterol, thiouracil, atropine, barbiturates and antihistamines. All stresses (surgery, emotional outbursts and upsets, acute pressures, extremes of heat and cold and all drugs) as well as alcoholic beverages are vitamin C antagonists. Anemia is often observed in vitamin C deficient patients. A normocytic or macrocytic anemia is generally observed, though megaloblastic has been reported sometimes in same patients. The presence of megaloblastic anemia in some scorbutic patients has given rise to the consideration that either a dietary deficiency of folic acid existed or that folate metabolism was impaired in vitamin C deficiency. In some instances the megaloblastic anemia was effectively treated with ascorbic acid alone, while in other reports, additional amounts of folic acid supplementation were required.
Vitamin E supports a healthy immune system and may help to protect against cardiovascular disease by decreasing atherosclerosis and helping the blood circulation. Because of these effects on the blood, taking vitamin E supplements may increase the risk of bleeding, especially in patients taking anticoagulant medications such as warfarin or patients of vitamin K deficiency.\textsuperscript{25}

Vitamin K is necessary for blood to coagulate effectively. Patients with a vitamin K deficiency have an increased risk of uncontrolled bleeding. There are some postulations which suggest that vitamin E inhibit the vitamin K dependent carboxylase activity and subsequently inhibit the coagulation cascade.\textsuperscript{32} Therefore, high amount of vitamin E decrease the activity of vitamin K in coagulation. \textit{α}-tocopheryl hydroquinone is an oxidized product of \textit{α}-tocopherol and an efficient antioxidant. Vitamin E quinine is a potent anticoagulant as inhibitor of vitamin K dependent carboxylase that controls blood clotting.\textsuperscript{15}

\textbf{B vitamin Antagonists}

Cortisone is an antagonist of vitamin B\textsubscript{6} (pyridoxine). Since the body needs B vitamins to metabolize sugars, B vitamins are depleted when refined sugar or flour is consumed as refined sugar and flour are devoid of B vitamins that existed in the beet, cane or grain before refining. Specifically, the body’s supply of vitamin B\textsubscript{1}, vitamin B\textsubscript{2}, biotin, choline, niacin and the mineral magnesium are depleted when refined sugar and flour are consumed. Alcoholic beverages are antagonists of thiamin and the other B-complex vitamins. Coffee is another popular beverage that is a B vitamin antagonist, because it contains caffeine and other noxious substances like chlorogenic acid. Inositol deficiency may occur among coffee drinkers along with deficiency of biotin and thiamin. Raw fish and raw shellfish, including oysters, are also B-complex antagonists as raw fish contains the enzyme thiaminase which destroys thiamine. This is one of many reasons not to eat the Japanese dish, sashimi (raw fish) or any other raw seafood.

The urinary excretion of 4-pyridoxic acid (the major metabolite of vitamin B\textsubscript{12}) was elevated with an increased intake of ascorbic acid.\textsuperscript{31}

The most potent folacin (folic acid) antagonist is aminopterin, a substance that has been used in the medical treatment of leukemia, a disease in which there is a marked increase in the production of leucocytes (white blood cells). Some research indicates that large doses of vitamin C block the absorption of vitamin B\textsubscript{12}.\textsuperscript{31}

\textbf{Vitamin Synergisms}

Synergy is defined as the combined interaction of several system elements which produces an entirely different or greater effect compared to what they produce by their separate effects. In many cases, a synergistic relationship between certain elements can produce long-term benefits.\textsuperscript{4}

Vitamins are involved in many reactions and also have beneficial effect or synergistic effect. They act as coenzymes and are involved synergistically in many enzymatic reactions. They can also protect against deficiencies of other vitamins.

\textbf{Table: 1 Different vitamin and their synergistic vitamins}\textsuperscript{35}

<table>
<thead>
<tr>
<th>Vitamins</th>
<th>Synergist Vitamins</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>B\textsubscript{1}, C-E, B\textsubscript{2}, B\textsubscript{3}, B\textsubscript{5}</td>
</tr>
<tr>
<td>D</td>
<td>B\textsubscript{12}</td>
</tr>
<tr>
<td>E</td>
<td>A-B\textsubscript{6}, C-B\textsubscript{2}, B\textsubscript{1}, B\textsubscript{5}, D</td>
</tr>
<tr>
<td>B\textsubscript{1}</td>
<td>E-C, B\textsubscript{2}, B\textsubscript{1}, B\textsubscript{5}, A-B\textsubscript{6}</td>
</tr>
<tr>
<td>B\textsubscript{2}</td>
<td>A-B\textsubscript{10}</td>
</tr>
<tr>
<td>B\textsubscript{3}</td>
<td>A-B\textsubscript{5}, B\textsubscript{6}</td>
</tr>
<tr>
<td>B\textsubscript{5}</td>
<td>B\textsubscript{12}, B\textsubscript{6}, E-B\textsubscript{6}, C-D</td>
</tr>
<tr>
<td>C</td>
<td>A-E, B\textsubscript{3}, B\textsubscript{5}</td>
</tr>
<tr>
<td>B\textsubscript{7}</td>
<td>B\textsubscript{2}, B\textsubscript{5}, A-B\textsubscript{6}, E</td>
</tr>
<tr>
<td>B\textsubscript{8}</td>
<td>C-E-A-B\textsubscript{6}, B\textsubscript{2}, B\textsubscript{5}</td>
</tr>
</tbody>
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Antioxidant vitamin supplementations may reduce the severity of trypanosome infection by offering protection against possible oxidative injuries associated with the disease\textsuperscript{33} and thus, beneficial in pregnancy related infections (malaria) and complication (hyperlipidemia). In the last 20 years, some clinical and epidemiological researches have suggested a potential protective effect of antioxidant nutrients such as beta-carotene, vitamin C, and vitamin E on the risk of cancer and cardiovascular diseases. Vitamin C can also regenerate oxidized Vitamin E by
reducing it back to its active form. The key step is the reaction between the tocopheroxyl radical and vitamin C. Vitamin C regenerates active vitamin E and increases cholesterol excretion. Plasma tocopherol levels also improved upon supplementation of vitamins E and C, this improvement suggests synergism of vitamin C with glutathione peroxides to revitalize vitamin E.

Vitamin K₂ (menaquinone) is responsible for activating certain proteins by adding CO₂ (carbon dioxide) to them. Vitamins A and D help body to absorb zinc which in turn enables body to absorb fat-soluble vitamins. Vitamins A, D, and K₂ work together to build strong bones and teeth, promote growth, protect against calcification of the soft tissues, and support immune system.

**Vitamin B synergism**

Vitamin B₁₂ supports the formation of healthy red blood cells. Taking folic acid (vitamin B₉) can mask the effects of megaloblastic anemia. The interaction between folic acid and vitamin B₁₂ can increase the effects of the anemia and lead to permanent neurological damage.

For the conversion of folic to folinic acid, vitamin B₁₂ is essential. Folic acid therapy of patients, suffering from sprue, causes an increase in plasma vitamin B₁₂ content. Vitamin B₁₂ deficiency causes a rise in unconjugated folates and depletion of intracellular conjugated folates.

Vitamin B₆, a member of the B family of vitamins along with B₁₂, promotes the production of hormones and neurotransmitters, the chemicals that carry signals between the nerves. Vitamin B₆ is also important for the production of healthy red blood cells because the presence of B₆ enhances the absorption of B₁₂.

Administration of thiamine, riboflavin and pantothenic acid offered partial protection from spontaneous seizures, which may be due to vitamin B₆ deficiency. A deficiency in vitamin B₆ can lead to a deficiency in B₁₂. In addition, vitamins B₆, B₁₂ and folic acid all work together to control the level of homocysteine, an amino acid associated with an increased risk for heart disease. Thiamine deficiency is often accompanied by disturbance of riboflavin metabolism, causing considerable excretion of riboflavin in urine. In another interaction, deficiency of pantothenic acid affects adversely the mobilization of riboflavin from the liver. Administration of pantothenic acid of deficient animals increases the mobilization of riboflavin from liver and raises the levels of riboflavin in blood.

The liver of rats fed on thiamine deficient or riboflavin deficient diets contained smaller amount of niacin than normal controls. Treatment of pellagra with niacin precipitates symptoms of thiamine and riboflavin deficiencies indicating that niacin deficiency is accompanied by secondary deficiency of thiamine and riboflavin.

Baker et al. followed whole blood ascorbic acid levels in normal adult men subjected to depletion and repletion of vitamin B₆. Whole blood level of ascorbic acid progressively fell during the vitamin B₆ depletion phase and returned to normal level upon repletion with pyridoxine. In a subsequent study on Vitamin C deficiency in adult men, the urinary excretion of free pyridoxine was measured. Vitamin B₆ deficiency has been reported to cause impairment in vitamin B₁₂ absorption in the rat, resulting in a lowering of vitamin B₁₂ levels in the serum and in reduced vitamin B₁₂ stores in the liver. The riboflavin deficiency in the rat slowed the uptake of labeled pyridoxine into the liver and decreased the conversion of pyridoxine to its metabolites.

**Interaction among vitamin C, vitamin E, and β-carotene**

The effects of vitamin C (ascorbic acid), vitamin E (α-tocopherol), and β-carotene as antioxidants and their cooperative action against the oxidation of lipid in solution, membranes, and lipoproteins have been studied and reviewed by Niki and associates. Ascorbic acid and α-tocopherol act as potent and probably the most important, hydrophilic and lipophilic antioxidants, respectively. They function at their own site individually and
furthermore act synergistically. β-carotene acts as a weak antioxidant in solution and has lower reactivity toward radicals than that of α-tocopherol\textsuperscript{23}.

**Some other interrelationship of vitamins:**

**Biotin and pantothenic acid:** Biotin deficiency may be aggravated by a simultaneous pantothenic acid deficiency. The addition of biotin to the diet not only protects the animals from biotin deficiency but also reduces the severity of the symptoms of pantothenic acid deficiency\textsuperscript{31}.

**Vitamin A, E and K:** It has been shown that albino rats fed on a vitamin K deficient diet develop signs of vitamin K deficiency when vitamin A in diet is increased. Considerable amount of work has been carried out by different workers on the role of vitamin E in influencing storage and mobilization of vitamin A in liver. Administration of vitamin E helps to increase the storage of vitamin A in liver\textsuperscript{31}.

**Ascorbic acid and other vitamins:** The albino rat can synthesize ascorbic acid. This synthetic capacity, however, is diminished considerably in thiamin and riboflavin deficiencies. This indicates that both these vitamins play an important role in the biosynthesis of ascorbic acid. A depletion of the ascorbic acid content of tissues of rats occurred when the animals were fed on diets deficient in vitamin A or thiamin or riboflavin\textsuperscript{31}.

**Folic acid and Vitamin B\textsubscript{12}:** For the conversion of folic to folinic acid, vitamin B\textsubscript{12} is essential. Folic acid therapy of patients, suffering from sprue, causes an increase in plasma vitamin B\textsubscript{12} content. Vitamin B\textsubscript{12} deficiency causes a rise in unconjugated folates and a marked depletion of intracellular conjugated folates.

**Vitamin B\textsubscript{12} and Vitamin C:** Vitamin B\textsubscript{12} is an important nutrient that plays a role in neurological function, the synthesis of DNA and the creation of red blood cells. Vitamin B\textsubscript{12} deficiencies result in numerous symptoms such as anemia and neurological problems. Herbert and Jacob\textsuperscript{12} reported that presence of ascorbic acid in meal destroys the vitamin B\textsubscript{12}, but the same report was not replicated during further study by Newmark \textit{et al.}\textsuperscript{22}. Again Herbert \textit{et al.}\textsuperscript{13} reported that some patients having spinal cord injury found to have deficient amount of vitamin B\textsubscript{12} after receiving ascorbic acid for a period of 2 years. Lucock \textit{et al.}\textsuperscript{18} reported that dietary vitamin C regulates red cell folate status of body either directly or indirectly protecting dietary 5-methyle-tetra hydro folate as vitamin C is an antioxidant. So it can be said that antioxidant vitamin C is critical in sparing highly labile trace levels of the natural 5-methyle- tetra hydro folate.

**CONCLUSION**

In human daily requirements of vitamins and minerals and very less and also considered as micronutrients. The understanding of nutrition and its important role in health is most important and intricate part of health care, particularly among today's progressive health care providers. Vitamin interrelationship with other nutrients and drugs are very important study for the nutrition science personnel to avoid unnecessary side effect of both deficiency and toxicity of micronutrients. Vitamin synergism action is very useful for the body proper mechanism action and also effective for other nutrients absorption in the body. Nutritional therapeutics has largely been directed towards the recognition and correction of nutritional deficiencies. It is now becoming evident that a loss of homeostatic equilibrium between the nutrients can also have an adverse effect upon health. A loss of this vital balance, particularly between the trace elements, can lead to subclinical deficiencies.

**REFERENCE**


