Multivitamins : Use or Misuse?

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Introduction

It has been more than a century since an Englishman, William Fletcher in 1905 while researching the cause of the disease Beriberi, discovered that it could be prevented by eating unpolished rice. He concluded that the husk of rice must have special nutrients, which we know today as vitamins. The term vitamin originated from "vitamine," a word first used in 1911 by the Polish scientist Casimir Funk to designate a group of compounds considered vital for life; each was thought to have a nitrogen-containing component known as an amine. The final "e" of vitamine was dropped when it was discovered that not all of the vitamins contain nitrogen and, therefore not all are amines.

Role of Vitamins

The thirteen essential vitamins are either fat soluble (A,D,E,K) or water soluble vitamins viz. C, B₁ (thiamine), B₂ (riboflavin), B₃ (niacin), B₆, B₁₂, pantothenic acid, biotin and folate (folic acid). Fat soluble vitamins are stored in the body for prolonged periods and as a class deal with the regulation of protein synthesis. Vitamin C and B-complex vitamins are stored to a limited extent

(except B₁₂) and frequent consumption is necessary.

B-complex vitamins generally form coenzymes and catalyse the oxidation of small molecules in the production of energy. Vitamin C is an anti-oxidant and plays a specific role in the hydroxylation of specific compounds [1,2]. A well balanced Indian diet is able to provide most vitamins and micronutrients except B₁₂ in strict vegetarians (Table 1).

Vitamins in therapeutic amounts (normally 5-10 times, the recommended daily allowance) are indicated for the treatment of deficiency states or pathologic conditions in which absorption and utilisation of vitamins is reduced or when requirements are increased [3]. In addition, they are also recommended for the treatment of non-nutritional disease in which a large dose has a unique effect independent of nutritive activity e.g. alcoholic neuritis and Wernicke's syndrome (thiamine), hyperlipoproteinaemias (niacin), to prevent neuropathy in those on isoniazid (pyridoxine), sideroblastic anemia (pyridoxine), infantile seborrhea (biotin) and acute promyelocytic leukaemia (all-trans-retinoic acid) [4-7].

The term multivitamin came into vogue sixty years

Table 1

Vitamin content of common Indian food items

Vitamin	Thiamine	Riboflavine	Nicotinic Acid	Vitamin C	Vitamin A	CaroteneIU ^b	Vitamin D
(Recommended daily allowance)	(1500) µg	(1700) µg	(19) mg	(60) mg	(1000) IU		(200) IU
Rice, milled, boiled 1 cup	27	11	1.0	-	-	-	-
Wheat chapatti 15g	45	45	0.9	-	-	-	-
Egg medium, boiled 48gms	40	130	1.6	-	550	-	27
Milk, cow, 1 cup	100	360	2.3	4	300	-	8
Bengal gram (chana dal) 1 cup	87	127	1.1	-	-	-	-
Black gram (urad dal) 1 cup	76	92	1.5	-	-	-	-
Lentil (masur dal) 1 cup	81	125	1.0	-	-	-	-
Cabbage, cooked, ½ cup	40	40	-	58	-	-	-
Carrot, raw 1 large	60	60	-	-	-	12000	-
Roast chicken 100 gms	80	180	13	-	-	-	-
Mutton, lean 30 gms	70	95	4.2	-	-	-	-
Ghee 1 teaspoon	-	-	-	-	165	-	5
Butter 1 teaspoon	-	-	-	-	165	-	2

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ago when Miles Laboratory, United States marketed a combination of Vit A, Vit D, β -carotene, B-vitamins and micronutrients (iron, calcium etc). Since then a number of combinations have been marketed as multivitamins [8]. The National Health and Nutrition Examination Survey (NHANES) USA, defines multivitamin as a formulation containing three or more vitamins with or without minerals [9]. These may be marketed as specialised products such as multivitamin for men, senior women, menopausal women, persons with diabetes, for energy, for hair growth and so on. The content of each multivitamin is determined by the manufacturer, e.g. a brand of multivitamin available in the Armed Forces contains 26 vitamins and micro nutrients (Table 2). The bioavailability of the individual vitamin or micronutrient in a multivitamin depends on the homeostatic mechanism which regulates absorption and excretion depending on level of nutrient in the host. It also depends on the dose of each vitamin/micronutrient in a preparation of multivitamin and the interaction of the various components, for instance vitamin C increases the bioavailability of iron.

Multivitamin as Health Promoter: Is it Evidence Based ?

Both observational studies and randomised controlled trials (RCT's) have been conducted for studying effect of single nutrient supplementation or multivitamins in healthy individuals. Antioxidants scavenge free radicals and other reactive oxygen species that damage cellular membranes, organelles and macromolecules. There has been an interest in assessing the role of antioxidants (vitamin C, vitamin E and β carotenes found in vitamin A preparation) in cardiovascular disease and cancer. Several studies have shown that vitamin E in doses higher than recommended daily allowance had cardio protective effect. Low density lipoprotein concentration decreased significantly in blood taken from subjects receiving >200 IU a day but not in those on < 200 IU a day. A double blind placebo controlled trial showed a significant decrease in non-fatal myocardial infarction in high risk subjects consuming either 400 or 800 IU

vitamin E/day as supplement. Vitamin E was also shown to be effective in prevention of cancer [1]. However, Lee et al [12], in a randomised controlled trial (Women's Health Study) using vitamin E 600 IU on alternate days in women >45 years, found no overall benefit for prevention of major cardiovascular diseases or cancer. The strength of the study lies in the fact that it involved a large population (39,876) studied over a long duration (10.1 years) of time.

In vitro observation and epidemiologic studies have shown that people with high intake of β carotene or high blood concentration of this nutrient have reduced risk of various diseases including cancer and heart disease. The effect has been attributed to antioxidant properties of β carotene. However when a RCT used β carotene and α tocopherol in Finnish smokers to test this hypothesis, there was an increase rather than decrease in the incidence of lung cancer in the β carotene group [13].

Higher intake of folate has been inversely associated with coronary heart disease (CHD), possibly due to decrease in homocysteine levels. The Nurses Health Study, a prospective cohort study of 1,21,700 nurses in the United States suggested that intake of folate and vitamin B₆ above the recommended dietary allowance may be beneficial for primary prevention of CHD among women. The primary sources of folate in this study were multivitamin and diet [14]. However a recent RCT has come up with contradictory evidence. A combination pill of folic acid (2.5mg), Vit B₆ (50 mg) and Vit B₁₂ failed to reduce cardiovascular events among high risk women despite reduction in homocysteine levels [15].

Selenium in doses of 200 μ g (thrice the recommended daily intake) was used in a multi centre double blind, placebo controlled trial to determine whether it decreased the incidence of cancer. After a follow up of 6.4 years, there was no decrease in the incidence of squamous or basal cell carcinoma (primary end point). However there was a significant reduction in cancer mortality, incidence of carcinoma of lung, prostate and colorectal carcinoma (secondary end point) [16]. This

Table 2
Nutrient content of "Standard" multivitamin tablet*

1. Vitamin A	2500 IU	11. Vitamin K	10 μ g	21. Chromium	25 μ g
2. Thiamine mononitrate	1 mg	12. Zinc	15 mg	22. Molybdenum	25 μ g
3. Vitamin B ₂	1.5 μ g	13. Potassium iodide	0.15 mg	23. Selenium	30 μ g
4. Vitamin B ₁₂	1 mg	14. Ferrous fumarate	10 mg	24. Nickel	5 μ g
5. Vitamin C	50 mg	15. Magnesium	100 mg	25. Tin	10 μ g
6. Vitamin D	200 mg	16. Manganese	2.5 mg	26. Silicon	2 mg
7. Alpha tocopherol	7.5 mg	17. Copper	2 mg	27. Vanadium	10 μ g
8. Calcium pantothenate	5 mg	18. Calcium	162 mg	28. Boron	150 μ g
9. Folic acid	15 mg	19. Potassium chloride	40 mg		
10. Nicotinamide	20 mg	20. Chloride	36.3 mg		

* Branded multivitamin tablet available at service hospital

is a solitary trial and needs confirmation.

As part of Women's Health Initiative (WHI), healthy post menopausal women received Vit D₃ (400 IU) and calcium carbonate (containing elemental calcium 1000 mg), with an aim to prevent hip and other fractures. At the end of study period there was a small but significant increase in bone mineral density (BMD), without any reduction in the incidence of hip fractures [17].

In a questionnaire study on apparently healthy individuals, 58% of respondents took multivitamins for prevention against chronic diseases and 32% took them for "feeling better" [8]. Single nutrient studies discussed above do not provide concrete evidence of benefit. The dose of these nutrients in multivitamin formulations is much less and it seems illogical to prescribe multivitamins to prevent chronic disease. Few trials have been conducted to study the effect of multivitamin supplementation in healthy individuals for prevention of chronic diseases. In Cancer Prevention Study II, a cohort of 10,63,023 adult Americans were examined prospectively to determine the relation between multivitamin use and mortality from heart disease, cerebrovascular accidents and cancers. Users of multivitamin had similar mortality due to cardiovascular disease and cancers as compared to non-users. There was a concern raised regarding increased mortality among male smokers [18]. Similarly Physicians Health Study observed a cohort of 83,639 US male physicians and found that use of vitamin E, vitamin C and multivitamin was not associated with any change in cardiovascular mortality [19].

Multivitamins are commonly used in residents of old age homes and in those who do not take adequate diet. Poor exposure to sunlight leads to lower 25 hydroxylated vitamin D levels and potentially increases the risk of fractures. Supplementation of calcium carbonate containing 1000 mg of elemental calcium and vitamin D has shown increased BMD, without decreasing the risk of fractures. The incidence of Alzheimer's disease (AD)

is increasing as a result of longer life span. Cross sectional and prospective studies have shown use of antioxidants in the form of Vit E and Vit C to reduce the severity and incidence of AD. Cache County Study, a cross sectional and prospective study has reported reduced risk of AD in users of vitamin E and multivitamins containing vitamin C [20].

The purpose of micronutrient supplementation in pregnancy is to improve pregnancy outcome and breast milk quality. For those who are well nourished and adhere to a balanced diet there is little need for multivitamin supplementation. The use of folate supplement in pre-conceptional stage is important to reduce the number of births with neural tube defects and in later part of pregnancy along with iron to prevent dimorphic anemia. There is some evidence that supplementation of calcium may decrease the incidence of pregnancy associated hypertension, pre-eclampsia and depression in population with low calcium intake [21].

Safety of Multivitamins

The misuse of vitamins is not without its safety concerns. The amount of vitamins or nutrients in multivitamins generally does not exceed the recommended daily allowance. For vitamins to cause side effects the intake should exceed recommended daily allowance several fold (Table 3). Excess intake may occur if single vitamins are taken in addition to multivitamins [22]. The vitamins and micronutrients for which excess intake has been reported are vitamin A, vitamin C, niacin, iron and zinc [23]. The common interactions with other drugs are those involving vitamin E and aspirin leading to increased antithrombotic effect and that between vitamin E and warfarin leading to increased likelihood of bleeding.

Discussion

From the above it is apparent that vitamins are indicated in therapeutic doses only in deficiency states and for certain nonnutritional diseases. They have role

Table 3
Potential toxic effects associated with select vitamin supplements*

Vitamin	Potential toxic effects associated with supplement
Vitamin A (retinol)	Hepatotoxic effects, visual changes, hair and skin changes, teratogenic effects at intake >1000-1500 IU/day; potential increased risk of hip fracture at intake >5000 IU/day
Beta carotene (provitamin A)	Risk of lung cancer among smokers and people with asbestosis at intake >3000 IU/day; yellowing of skin, diarrhea and arthralgias
Vitamin C (ascorbic acid)	Diarrhea, gastric upset at intake >2000mg/day
Vitamin D	Soft tissue calcification or hypercalcemia at intake >2000 IU/day
Vitamin E	Nausea, vomiting, diarrhoea, possible antiplatelet effects, headache fatigue and blurred vision at intake > 800 IU/day
Vitamin B ₆ (pyridoxine)	Sensory neuropathy, ataxia if regular intake >200 mg/day
Vitamin B (cyanocobalamin)	No upper limit known.
Niacin (vitamin B)	Vasodilatation, gastrointestinal upset, hyperglycemia, potential interactions with statins, antihypertensive drugs; hepatotoxic effects may occur at intake >3000 mg/day

Table 4**Percentage of prescriptions with multivitamins**

1. Diagnosis not specified	- 39.3 %	5. Myalgia, Low backache	- 5.1 %
2. Type 2 Diabetes mellitus Hypertension, CAD	- 20.5 %	6. Aphthous Ulcer	- 2.4 %
3. Miscellaneous ¹	- 6.8 %	7. Malignancies ³	- 2.4 %
4. Skin diseases ²	- 6.2 %	8. Antenatal care	- 1.6 %

1. Acute gastroenteritis, anxiety, depression, bronchial asthma, giddiness, weakness.

2. Seborrhoeic dermatitis, urticaria, alopecia.

3. Post operative malignancies (thyroid, breast and cervix).

as prophylaxis in pregnancy and possibly in elderly. However when used to prevent disease not much is to be gained if a person is eating a healthy, balanced diet and has no absorptive defect. Yet the multivitamin industry is thriving. One reason is the easy availability of these preparations over the counter or as one author put it from “brick and mortar shops”. In a questionnaire study, the Hawaii Los Angeles Multi Ethnic trial (MEC); of the 1,00,196 respondents, 48 % of men and 56% of women reported using multivitamin at least once weekly for the preceding year [23]. In another study multivitamins were more likely to be used by women, individuals from older age group, with higher educational level and low BMI. These were the individuals who would be health conscious and be involved in health promoting activities [9].

The question arises regarding our position in the Armed Forces: Do we use or abuse multivitamins? The authors conducted a survey of 2000 prescriptions containing multivitamins prescribed over a span of two months from a tertiary level Armed Forces hospital. The findings are as shown in Table 4. Multivitamins had been prescribed for all possible ailments encountered in practice. There appeared to be no scientific rationale for prescriptions of multivitamins and they seem to be prescribed like a placebo. The common brands of vitamins prescribed were Polybion, Zevit, Becosule and Rivonia. We did a rough costing of the multivitamins. The cost of each tablet of multivitamin preparation ranged from Rupees (Rs) 1 to 5. The cost of the multivitamin preparation in Table 2 was Rs 4.50 per tablet. If the vitamins were prescribed for a month, the average expenditure incurred over one year would be approximately Rupees Thirty two lacs and forty thousand. If one were to extrapolate this figure to other major hospitals, there would be a staggering expenditure of approximately Rupees Two crores. The drawback of the above calculation is that we have used the most expensive brand, while the number of prescriptions and the duration of therapy is an approximation. In addition, the procurement price may be different from the retail price. However the discussion shows that we are spending significant amount of money on a medicine, which has no significant benefit in most patients.

It would not be incorrect to conclude that the current data does not support the nonspecific use of multivitamin, in the absence of deficiency states and that specific vitamin/mineral supplements rather than multivitamins should be used where indicated.

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Conflicts of Interest

None identified

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Answer to Radiological Quiz

Intraosseous Lipoma of the Calcaneum

Fig. 1 : Radiograph heel axial and lateral view showing osteolytic lesion at the base of neck of calcaneum with septations.

Fig. 2 : Axial CT of calcaneum shows osteolytic lesion with negative Hounsfield unit consistent with fat density and central calcified spur.

Discussion

Intraosseous lipoma is an extremely uncommon entity despite the large amount of adipose tissue present in the bone marrow [1]. It is rare, with an incidence of less than 1 per 1000 of bone tumours [2]. Intraosseous lipoma primarily involves the lower extremities. They are most commonly reported in the metaphysis of the long bones, especially the femur, and to a lesser extent in the calcaneus. In the calcaneus, these lesions are located at the base of the neck of the calcaneus (Ward's triangle) [3]. In 33% of cases, intraosseous lipoma is found incidentally [3]. In the remaining cases, pain is the most common presenting symptom. The presence of pain does not imply the presence of a pathological fracture. Patients usually present as middle-aged adults, with an average age of 40 years as seen in this case. Males and females are equally affected. The radiographic appearance of a well-circumscribed lytic lesion, with a central nidus of calcification and surrounding thin sclerotic rim, is diagnostic of an intraosseous lipoma [4]. The differential diagnosis for the radiographic appearance of the intraosseous lipoma of the calcaneus includes aneurysmal bone cyst, giant cell tumour and unicameral bone cyst [4]. Advanced imaging with computed tomography (CT) or magnetic resonance imaging (MRI) can establish the diagnosis

easily as both methods show fat-equivalent densities in the lesion. CT demonstrates a lytic lesion with negative Hounsfield units (HU), typically around -20 to -30 HU as seen in this case. CT is also useful in detecting pathological fracture and excluding an associated soft tissue mass [3]. On MRI, the intraosseous lipoma may be well-circumscribed or have ill-defined margins. They appear bright on short repetition time (TR)/short echo time (TE) spin echo sequences, intermediate on long TR/long TE spin echo sequences, and dark on fat-suppression sequences [5]. Curettage and packing of an intraosseous lipoma is indicated in the setting of a painful lesion. The goal of surgery is to relieve pain and to prevent a pathological fracture, especially when the lesion is located in a weight-bearing bone. Non-painful lesions may be treated conservatively as they may undergo spontaneous involution.

Conflicts of Interest

None identified

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