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The role of vitamins in prevention of non-communicable diseases (NCDs): A review

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Abstract
Non-communicable diseases (NCDs), also known as chronic diseases, tend to be of long duration and are the result of a combination of genetic, physiological, environmental and behavioral factors. The main types of NCDs are cardiovascular diseases (like heart attacks and stroke), cancers, chronic respiratory diseases (such as chronic obstructive pulmonary disease and asthma) and diabetes. Modifiable behaviours, such as tobacco use, physical inactivity, unhealthy diet and the harmful use of alcohol, all increase the risk of NCDs. Metabolic risk factors contribute to four key metabolic changes that increase the risk of NCDs: raised blood pressure, overweight/obesity, hyperglycemia (high blood glucose levels) and hyperlipidemia (high levels of fat in the blood). Observational studies (case–control or cohort design) have stated that people with high intake of antioxidant vitamins generally have a lower risk of myocardial infarction and stroke than people who are low-consumers of antioxidant vitamins. High intake of food items rich in flavonoids, that are powerful scavengers of free radicals (red wine, tea, onions and apples), have been associated with a low risk of cardiovascular disease. Vitamin C, D and E are reported to be involved in the amelioration of side effects which occur in chemotherapy and radiation therapy of lungs, stomach, prostate, colorectal, gastric head and neck cancers. Calcitriol (1, 25 (OH) 2D3) plays an essential role in a wide range of actions which include cell growth regulation, immune modulation and apoptosis, etc. Various cross-sectional and longitudinal cohort studies have indicated a beneficial effect from vitamin D supplementation on the development of type-2 diabetes.

Keywords: Prevention of NCDs, role of vitamins

Introduction
Non-communicable diseases (NCDs) encompass a vast group of diseases such as cardiovascular diseases, cancer, diabetes and chronic respiratory diseases. According to WHO, non-communicable diseases (NCDs), also known as chronic diseases, tend to be of long duration and are the result of a combination of genetic, physiological, environmental and behaviour factors. NCDs contribute to around 38 million (68%) of all the deaths globally and to about 5.87 million (60%) of all deaths in India. Four NCDs mainly responsible for the total NCD mortality and morbidity are cardiovascular diseases, chronic respiratory disease, cancers and diabetes, contributing to about 82% of all NCD deaths (WHO, 2014) [11].

NCDs disproportionately affect people in low- and middle-income countries (LMICs) where more than three quarters of global NCD deaths – 32 million – occur. 15 million of all deaths attributed to NCDs occur between the ages of 30 and 69 years. Of these "premature" deaths, over 85% are estimated to occur in low- and middle-income countries. In India, 5.8 million people die from NCDs every year before they reach 70 years of age (WHO report, 2015).

The World Health Organization's (WHO) Prioritized Research Agenda for the Prevention and Control of Non-communicable Diseases (NCDs) identified key areas of research relating to the prevention and control of NCDs (Mendis and Alwan, 2011) [6]. The epidemic of NCDs is rapidly emerging in many low and middle income countries (LMICs). Current evidence shows that 80% of NCD -related deaths occur in LMICs and, more than three quarters of 'premature' NCD deaths occur in LMICs (Smeeth and Ebrahim, 2005) [8]. As the magnitude of the epidemic in these countries is expected to increase in the coming years, increasing evidence is being generated on the nature and the scale of this epidemic, the characteristics of the various risk factors, and the social and economic impacts of NCDs (Ebrahim *et al*., 2013) [3].

Risk factors
A risk factor is defined as "An aspect of personal behavior or lifestyle, an environmental exposure, or a hereditary characteristic that is associated with an increase in the occurrence of

particular disease, injury, or other health condition" (Centers for Disease Control and Prevention, 2006) [2].

1. Modifiable behavioural risk factors

Modifiable behaviours, such as tobacco use, physical inactivity, unhealthy diet and the harmful use of alcohol, all increase the risk of NCDs. Tobacco accounts for over 7.2 million deaths every year (including from the effects of exposure to second-hand smoke), and is projected to increase markedly over the coming years (1). 4.1 million annual deaths have been attributed to excess salt/sodium intake (1). More than half of the 3.3 million annual deaths attributable to alcohol use are from NCDs, including cancer (2). 1.6 million deaths annually can be attributed to insufficient physical activity (1).

2. Metabolic risk factors

Metabolic risk factors contribute to four key metabolic changes that increase the risk of NCDs: raised blood pressure, overweight/obesity, hyperglycemia (high blood glucose levels) and hyperlipidemia (high levels of fat in the blood). In terms of attributable deaths, the leading metabolic risk factor globally is elevated blood pressure (to which 19% of global deaths are attributed), (1) followed by overweight and obesity and raised blood glucose.

An increase in the prevalence of overweight and obese individuals from 7% in 1975-79 to 24% in 2011-12 in National Nutrition Monitoring Board Surveys was noted by Meshram *et al*. (2015) [7] and from 10.6% and 1.6% in 1998–99 to 12.6% and 1.5% in 2005-06, in women and pre-school children respectively, in NFHS by Wang *et al*. (2009) [10].

Prevention and control of NCDs

The 2030 Agenda for Sustainable Development recognizes NCDs as a major challenge for sustainable development. As part of the Agenda, Heads of State and Government committed to develop ambitious national responses, by 2030, to reduce by one-third premature mortality from NCDs through prevention and treatment.

Antioxidant vitamins in the prevention of cardiovascular disease

A systematic review by Asplund (2002) [1], states that in observational studies (case–control or cohort design), people with high intake of antioxidant vitamins generally have a lower risk of myocardial infarction and stroke than people who are low-consumers of antioxidant vitamins. In randomized controlled trials, however, antioxidant vitamins as food supplements have no beneficial effects in the primary prevention of myocardial infarction and stroke. A low risk of cardiovascular death in subjects with a high intake of ascorbic acid was first reported in the 1950s. Ecological studies performed in the United Kingdom later reported a high mortality in myocardial infarction and stroke in areas with a low consumption of fresh fruit and vegetables. Patients with myocardial infarction have been observed to have low tissue content of lycopene, considered as a biomarker for intake of vegetable. There have also been reports on a particularly low risk of cardiovascular disease amongst high-consumers of nuts (which are rich in tocopherol). Furthermore, high intake of food items rich in flavonoids, that are powerful scavengers of free radicals (red wine, tea, onions and apples), have been associated a low risk of cardiovascular disease.

In a randomized control trials (RCT), an antioxidant cocktail with β-carotene, ascorbic acid, α-tocopherol and selenium reduced platelet aggregation. Platelet adhesiveness to the vessel wall is profoundly reduced also in healthy individuals when tocopherol is taken in doses around 400 mg daily.

Within a large cohort study, carotid intima-media thickness did not correlate with plasma levels of β-carotene or α-tocopherol, but there was an inverse relationship with lutein and zeaxanthin, carotenoid compounds that are regarded as biomarkers of fruit and vegetable intake.

Four studies reported a statistically significant inverse relationship with the risk of CVD events and, when all studies were taken together, high intake of tocopherol was associated with a highly significant reduction of cardiovascular events when compared with low intake, the odds ratio being 0.74.

Huffman *et al*. (2011) [13] stated that 14.3% of high income families in China experienced some form of household income loss due to cardiovascular disease (CVD) hospitalization, rising to 26.3% in India to 63.5% in Tanzania and to 67.5% in Argentina. This impact was patterned by socio-economic position, as greater household CVD-attributable income losses were reported for lower income groups (Campbell *et al*., 2011) [14]. In the USA, 10.4% of CHD patients reported that object oriented programme (OOP), spending was more than 20% of the family income (Engelgau *et al*., 2012) [15]. CVD patients in India spent 30% of their annual family income on direct CVD health care, where mean OOP per hospitalization increased from 364 USD in 1995–575 USD in 2004 (Rao *et al*., 2011) [16]. In CVD-affected households in India (30% borrowed or sold assets to pay for inpatient treatment, compared to 12% in matched control households (Karan *et al*., 2014). Also in India, the risk of impoverishment due to CVD was 37% greater than for communicable diseases.

Low-dose B vitamins supplementation ameliorates cardiovascular risk: a double-blind randomized controlled trial in healthy Chinese elderly

Wang *et al*. (2015) [9], investigated whether daily supplementation with low-dose B vitamins in the healthy elderly population improves the Framingham risk score (FRS). Between 2007 and 2012, a double-blind randomized controlled trial was conducted in a rural area of North China. 390 healthy participants aged 60–74 were randomly allocated to receive daily vitamin C (50 mg; control group) or vitamin C plus B vitamins (400 μg folic acid, 2 mg B6, and 10 μg B12; treatment group) for 12 months.

Results indicated that folate and vitamin B12 plasma concentrations in the treatment group increased by 253 and 80%, respectively, after 6 months, stopped increasing with continued supplementation after 12 months and returned to baseline levels 6 months after supplementation cessation. Compared with the control group, there was no significant effect of B vitamin supplementation on FRSs after 6 months, whereas a significant effect of supplementation was evident after 12 months B vitamins increased HDL cholesterol by 3.4% after 6 months and by 9.2% after 12 months.

Vitamins and cancer

Vitamin C, D and E are reported to be involved in the amelioration of side effects which occur in chemotherapy and radiation therapy of lungs, stomach, prostate, colorectal, gastric head and neck cancers. The vitamins acting as antioxidant adjuvants are found to have apoptotic and anti-

angiogenesis potential as well as inhibitory effects against metastasis in cancer cells.

Epidemiological, preclinical, and clinical studies furnish a support for the hypothesis that vitamins like vitamin D and A have a substantial protective action against cellular transformation which leads to cancer whereas the anticancer activities of vitamins B, C, E and K are quite limited.

Mechanisms of anticancer actions of vitamins

Calcitriol (1, 25 (OH) 2D3) plays an essential role in a wide range of actions which include cell growth regulation, immune modulation and apoptosis, etc. Numerous genes that are implicated in transformation of cancer are regulated by calcitriol. For example, 'Gatekeeper' genes such as p21 and p16 rule the entrance of the cell into the cell cycle. The 'gatekeepers' cease the cell from multiplying in case if a cell is damaged till it can either be mended or eradicated via apoptosis. 'Caretaker' genes, such as BRCA1 and BRCA2 are responsible for the regulation of the cell's capacity to repair damage. When these genes are either deleted or deactivated, further mutations take place and are propagated.

Vitamins decrease lung cancer risk by 50%

Johanson (2010) [5] researched the effect of B vitamins on a large group of participants and reported an inverse relationship between blood serum levels of vitamin B6, methionine, and folate and the risk of lung cancer.

The study gathered information about the lifestyle and diet of 385,000 people in several European countries. The average age was 64 years, and most had a history of drinking alcohol daily. Blood samples were then taken from these participants, and some of those (889) that developed lung cancer were analyzed for the level of several B vitamins and related biochemicals such as methionine, an essential amino acid. These nutrients were studied because they are known to be important in the metabolism of single carbon compounds, which is necessary for the synthesis and repair of DNA in the body's tissues. Thus, B vitamins are helpful in preventing defects in DNA which can cause cancer.

The study divided the participants into three categories, depending on whether they currently smoked, had previously smoked, or had never smoked. While smoking is the most important lifestyle factor in the risk for lung cancer, interestingly, the effects of vitamin B6, methionine, and folate were fairly constant among the three categories. That is, those with higher levels of these B vitamins had a significantly lower risk of lung cancer no matter whether they smoked or not. The report emphasizes that this result strongly suggests that the effect of these essential nutrients in lowering the risk for cancer is real and not purely a statistical correlation. And, the report reiterates that smoking is dangerous, greatly increasing the risk for lung cancer in older people after decades of insult to the lungs.

Mechanism of action: B Vitamins, including B6 and folate (B9), as well as related enzymes in the 1 carbon pathway, are essential for DNA synthesis and methylation. The 1-carbon metabolism process is complex and involves multiple interactions between B vitamins, homocysteine, and methionine, which in turn are required for generation of S-adenosyl methionine, an essential component of methylation reactions. Deficiencies in B vitamins may increase the probability of DNA damage and subsequent gene mutations, and may influence gene expression via aberrant methylation patterns. Given their involvement in maintaining DNA integrity and gene expression, these nutrients have a potentially important role in inhibiting cancer development, and offer the possibility of modifying cancer risk through dietary changes. Majorsourcesof1-carbonnutrientsand related vitamins are varied and include fruits and green leafy vegetables (folate), fortified cereals and wholegrains (B6), as well as meat and dairy products (B12).

Vitamins and diabetes

The micro- and macro-vascular complications of diabetes contribute to its morbidity and mortality. High blood glucose concentration promote auto-oxidation of glucose to form free radicals. Zhang *et al*. (2016) [12] stated that ample non-human experimental evidence has demonstrated that dietary antioxidants such as vitamins C and E and flavonoids, protect against free radical-mediated damage by reducing free oxygen radicals and replenishing antioxidant reserves. Various cross-sectional and longitudinal cohort studies have indicated a beneficial effect from vitamin D supplementation on the development of type-2 diabetes.

Those with low vitamin D levels tend to progress more rapidly to diabetes, possibly mediated through increased insulin resistance and poorer β-cell function. All-trans retinoic acid, a derivative of vitamin A, increases insulin sensitivity. Biotin also regulates the synthesis of insulin by the islet of Langerhans cells of the pancreas. The increase in advanced glycation end products (AGEs) is implicated in the initiation and progression of diabetes-associated microvascular diseases. Benfotiamine, a derivative of thiamine, and pyridoxamine, a vitamer of vitamin B6, both have anti-AGE properties.

Vitamins and chronic respiratory diseases

Recommended Dietary Allowance (RDA) of 600-800 IU is recommended to maintain adequate levels of vitamin D. ICMR recommends a daily supplement of 400 IU/day under situations of minimal exposure to sunlight. Evidence from population studies shows a higher prevalence of vitamin D deficiency in children with asthma compared with that in controls. Children with vitamin D deficiency also have reduced lung function, increased bronchial reactivity to exercise and an increased need for inhaled corticosteroids. The higher incidence of respiratory infections during winter has served as the basis for a hypothetical relationship between vitamin D levels and increased susceptibility to respiratory infections. Vitamin D has a modulating action on various cellular and molecular mediators involved in the inflammatory response to various stimuli. As in other respiratory infections, vitamin D plays an important role in the immune response against Mycobacterium tuberculosis infection.

In human beings, observational studies have associated vitamin D deficiency with an increased risk for different inflammatory, infectious, and autoimmune diseases. Vitamin D deficiency contributes to the pathophysiology of COPD through its effects on airway smooth muscle and lung remodulation by its actions on fibroblast proliferation, collagen synthesis and modulation of matrix metalloproteinase levels. With regard to chronic obstructive pulmonary disease (COPD), conflicting data have been reported.

Conclusion

Non-communicable diseases (NCDs) account for the leading cause of mortality globally. NCDs are a global epidemic because of the combined effect of the modern diet and a sedentary lifestyle. The causes are preventable. One of the principal policies to reduce the implications of NCD risks is to avert or lessen modifiable risk factors which will also prove more cost effective than providing curative services to people with NCDs. Numerous studies have indicated the effects of Vitamins such as A, C, D and E in lowering the risk of CVDs and cancers. B vitamins are helpful in preventing defects in DNA which can cause cancer. Various cross-sectional and longitudinal cohort studies have indicated a beneficial effect from vitamin D supplementation on the development of type-2 diabetes. The Investments in research are required to bring about the evidence base for selecting and implementing NCD programs and policies that are guided by a national research agenda for the prevention and control of NCDs in India.

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