CONSENSUS STATEMENT

Fortifying Micronutrient Supplementation in India: Expert Consensus by the American College of Physicians (India Chapter)

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ABSTRACT

Micronutrients play a key role in human health, being involved in energy metabolism, immunity, cellular functioning, growth, and development. Deficiencies in micronutrients occur in individuals of all ages due to several factors, including inadequate diets, disease states, and overweight/obesity. Guidelines from the Indian Council of Medical Research (ICMR) National Institute of Nutrition (NIN) Expert Group on Nutrient Requirements for Indians (2023) have specified the Recommended Dietary Allowances (RDA) for macronutrients and micronutrients. In addition, a healthy diet is crucial for overall health and should be the first step toward addressing micronutrient deficiencies. When diet is inadequate, micronutrient supplements can be provided to compensate. An expert panel of Indian doctors, including those affiliated with the American College of Physicians, was convened to develop a pathway toward micronutrient supplementation among the Indian population. This Consensus Statement recognizes that different populations have varying needs for specific micronutrients, and ensuring adequate intake of such micronutrients can improve health outcomes. The panel provided recommendations for dietary practices and micronutrient supplementation when diet is inadequate. Addressing micronutrient deficiencies at the primary care level can prevent chronic deficiencies and their consequences. This Consensus Statement can serve as a primer for physicians to monitor and address deficiencies and thus help individuals maintain their health.

INTRODUCTION

Micronutrients play a crucial role in human growth and development and are also required for normal functioning, energy metabolism, and immune function. Micronutrients, including vitamins and minerals, are dietary components that do not contribute to caloric intake but are necessary for health and vital functions. Micronutrient inadequacy is the intake of nutrients in lesser quantity than the estimated average requirement and can present with covert symptoms that are difficult to identify. Unidentified and untreated deficiencies could contribute to the development of chronic diseases.

Malnutrition is defined by the World Health Organization (WHO) as “deficiencies or excesses in nutrient intake, imbalance of essential nutrients or impaired nutrient utilization.” It encompasses undernutrition (wasting, stunting, underweight, and micronutrient deficiencies), overweight, and obesity. Micronutrient deficiencies occur in obese and overweight individuals as well, driven by the consumption of calorie-rich, nutrient-deficient foods, excess adipose tissue, altered metabolism and distribution of nutrients, and increased requirements for micronutrients.

ROLE OF MICRONUTRIENTS IN HEALTH

The complex process of energy metabolism in the human body requires a plethora of enzymes, and micronutrients function as cofactors for enzymes and participate in proton transfer. Micronutrient deficiencies impact cardiorespiratory function during exercise as well as submaximal work. Micronutrients play a vital role in cell proliferation, growth, apoptosis, wound healing, replication, transcription, translation, gene expression, gene regulation, skeletal muscle function, neuromuscular conduction, myocardial contraction, maintenance of blood pressure, protein and nucleic acid synthesis, bone mineralization, and regulating active transmembrane transport of various cations and anions, etc.

Micronutrient inadequacy can lead to specific diseases (anemia, goiter, etc.) as well as impaired learning, stunted growth, and premature death. Around 45% of deaths in children aged under 5 years can be attributed to micronutrient deficiencies. The complex, integrated immune system needs multiple specific micronutrients, which play vital and often synergistic roles at every stage of the immune response (Table 1). Supplementation with multiple micronutrients that have immune-supporting roles may modulate immune function and reduce the risk of infection. There is, thus, a need for comprehensive nutritional care to prevent disease in the general population.

SCOPE OF THE CONSENSUS

This Consensus Statement was developed by an expert panel of doctors (physicians, endocrinologists, diabetologists, cardiologists, and nutritionists) to develop a pathway toward micronutrient supplementation in the Indian population. This Consensus Statement takes cognizance of the fact that different populations have varying needs for specific micronutrients, and ensuring adequate intake of such micronutrients can improve health outcomes.

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**Understanding Micronutrient Deficiencies in India**

During 2014–2016, 14.5% of the Indian population (190.7 million people) were undernourished. Micronutrient deficiencies were the cause of 0.5% of deaths that occurred in 2016. In addition, micronutrient deficiencies cost up to 2.5% of the gross domestic product (GDP) of India.

### Mineral Deficiency and Disease

Magnesium deficiency has been reported in 44% of patients with type 2 diabetes mellitus (T2DM), and low serum magnesium levels are associated with poorer glycemic control and complications of diabetes. Hypomagnesemia is reported in ~63% of patients with nonproliferative diabetic retinopathy (NPDR). Indian patients with prediabetes have significantly lower serum levels of magnesium, selenium, and zinc compared with individuals without prediabetes. Levels of these minerals were negatively correlated with fasting plasma glucose (FPG), insulin, and insulin resistance, while glycated hemoglobin (HbA1c) correlated negatively with serum zinc and magnesium levels.

**Postmenopausal women** with osteoporosis have low levels of serum magnesium (1.95 ± 0.44 mg/dL). Levels of magnesium are indicators of the severity of asthma in adult Indians, with hypomagnesemia reported in nearly 59% of asthma patients (vs 5% of controls). Selenium deficiency has been reported in adult Indians with asthma, and levels of serum selenium correlate with the severity of the disease. Copper deficiency is reported in Indians with aplastic anemia, and serum copper levels are significantly reduced in patients with chronic obstructive pulmonary disease (COPD).

### Micronutrient Deficiency in Geriatric Patients

Geriatric individuals in India have inadequate micronutrient intake, which could be attributed to the poor quality of their diets. The prevalence of inadequate intake (<100% of recommended dietary allowances (RDA)) was reported for magnesium (48%), copper (81%), chromium (89%), thiamine (33%), and niacin (88%). Nutritional inadequacy was higher among geriatric subjects of lower socioeconomic strata. Vitamin D sufficiency has been reported in 22.64% of elderly individuals with coronary artery disease and in 51.04% of healthy elderly individuals. Geriatric Indian women with vitamin D deficiency have an increased risk of pelvic floor disorders, and patients with urinary incontinence had significantly lower serum vitamin D levels than those without (11.26 ± 6.3 vs 14.58 ± 7.29 ng/mL, p = 0.046).

### Obese Individuals

Young obese individuals with nonalcoholic fatty liver disease (NAFLD) have significantly lower levels of serum vitamin D than controls without NAFLD (17.21 ± 6.34 vs 26.56 ± 10.63 ng/mL, p < 0.001) and low serum vitamin D was independently associated with the risk of developing NAFLD (odds ratio 1.52). Metabolic syndrome is associated with vitamin D levels in obese Indians.

### Urban and Rural India

Studies on the micronutrient status of rural Indians have revealed the prevalence of vitamin B12 deficiency to be 42.3% without a significant difference between males and females, but females aged 45–54 years had a higher prevalence of deficiency. Among urban Indians, vitamin B12 deficiency was noted in 35.5% of individuals. The probability of adequacy for zinc was 11%, riboflavin, 37%, and thiamine 58%. Subjects with micronutrient inadequacy had a higher risk of iron-deficiency anemia and folate deficiency. Among healthy urban Indians, men were more likely to have inadequate levels of vitamin A, riboflavin, vitamin C, and zinc compared with women.

### Hair Loss

Nutritional deficiencies are prevalent among individuals with hair loss. Among patients with male pattern hair loss, 11.76% have zinc deficiency, and 29.41% have copper deficiency. Nearly 32% of patients with telogen effluvium have copper deficiency. In addition, more patients with telogen effluvium have iron deficiency compared to those with androgenetic alopecia.

### Deficiency of B Vitamins

A meta-analysis reported that folic acid deficiency is present in 41%, vitamin B12 deficiency in 48%, and vitamin D deficiency in 60% of Indians aged over 18 years. The National Family Health Survey-5 (NFHS-5) reported anemia among 57% of women and 25.0% of men aged 15–49 years. Overall, 52.2% of pregnant women, 57.2% of non-pregnant women aged 15–49 years, and 61% of breastfeeding women were anemic. Anemia was more common in women and men in rural areas compared to urban areas (women—59 vs 54%; men—27 vs 20%). Vitamin B12 deficiency is reported in individuals with NAFLD, with mean serum levels of 377.6 ± 181.4 pg/mL compared with 548.28 ± 285.7 pg/mL in non-NAFLD individuals. Thiamine deficiency has been reported in 67% of patients with heart failure (mean serum levels 1.02 ± 1.65 ng/mL) who were on long-term treatment with loop diuretics.
Fortifying Micronutrient Supplementation in India

**NUANCES OF INDIAN DIETARY HABITS CONTRIBUTE TO MICRONUTRIENT DEFICIENCIES**

Micronutrient deficiencies in India can be attributed to poor dietary habits and inadequate diet. Current diets in most Indian states are lacking in 11 of the 25 essential nutrients. In almost all states, the intake of riboflavin, fiber, potassium, and vitamin A is <50% of the RDA levels. Diets in east and northeast India are deficient in more nutrients compared with diets in other zones. Indian diets are predominantly cereal-based. However, cereals such as rice and wheat usually have inadequate micronutrient content (iron, calcium, vitamin A, riboflavin, and folic acid). It is alarming that 54–70% of households consume less than the recommended dietary intake (RDI) of green leafy vegetables, milk, and milk products.

Dietary patterns in India are linked to family values and cultural/religious beliefs. It is estimated that approximately one-third of the Indian population is vegetarian. While vegetarians consume greater quantities of legumes, pulses, and vegetables with lower quantities of fat compared with nonvegetarians, vegetarian diets do not provide adequate quantities of vitamin B12, omega-3 fatty acids, zinc, and other minerals. Additionally, poor absorption of zinc and iron has been reported for vegetarian diets compared with nonvegetarian diets, thus contributing to deficiencies.

Diets focusing on weight reduction coupled with improper dietary practices also lead to micronutrient deficiencies. The increased consumption of junk food and unhealthy snacking habits are also causative factors. The increased intake of processed foods, along with cereal-based food practices, are also causative factors.

**Multimicronutrient Deficiencies**

Worldwide, about 2 billion people are deficient in one or more micronutrients. In India, at least one, two, or three deficiencies have been reported in 41, 23, and 2.9% of pregnant women (tested for selenium, zinc, copper, iodine, vitamin B12, and ferritin). Hematopoiesis requires not only iron but folate and vitamin B12 as well. A study in India reported that adolescents with anemia were deficient in vitamin B12 but not in folate. A community-based study in north India reported that iron, folate, and vitamin B12 deficiency was present in 67.7, 26.3, and 74.1% of pregnant women, respectively, while concomitant deficiencies of these micronutrients were reported in 16.2% of the women. Another study reported that women with folate deficiency have a twofold higher prevalence of vitamin B12 deficiency.

**Association between Micronutrient Deficiency and Diseases**

The causal relationship between micronutrient deficiencies and disease has been studied extensively, with the deficiencies playing crucial roles in the development of disease. Conversely, disease states are also demonstrated to cause deficiency of specific micronutrients (Table 2).

**Treatment-associated Risk of Micronutrient Deficiency**

Drug-induced nutrient deficiencies can be categorized as adverse reactions (Table 3). These deficiencies occur due to the prolonged duration of drug therapy.

<table>
<thead>
<tr>
<th>Drug/treatment</th>
<th>Micronutrient deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRRT</td>
<td>Copper, selenium, vitamin C, folate, thiamine, and carnitine</td>
</tr>
<tr>
<td>Proton pump inhibitors</td>
<td>Vitamin B12</td>
</tr>
<tr>
<td>Metformin (especially chronic use and high-dose metformin)</td>
<td>Vitamin B12</td>
</tr>
<tr>
<td>Loop diuretics</td>
<td>Vitamin B1, calcium, and magnesium</td>
</tr>
<tr>
<td>Thiazide diuretics</td>
<td>Zinc, magnesium</td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>Calcium</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>Niacin, pyridoxine</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>Carnitine</td>
</tr>
<tr>
<td>Methotrexate, pentamidine, sulfasalazine, phenytoin, cholestyramine</td>
<td>Folate</td>
</tr>
<tr>
<td>Statins</td>
<td>Coenzyme Q10</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>Zinc</td>
</tr>
</tbody>
</table>

ACE, angiotensin-converting enzyme; CRRT, continuous renal replacement therapy

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**Table 2: Micronutrient deficiencies leading to disease, and diseases that cause micronutrient deficiency**

<table>
<thead>
<tr>
<th>Micronutrient deficiency</th>
<th>Subsequent disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin B1</td>
<td>Anemia, heart failure, and sarcopenia</td>
</tr>
<tr>
<td>Vitamin B2</td>
<td>Heart failure, sarcopenia</td>
</tr>
<tr>
<td>Vitamin B3</td>
<td>Anemia, hypertension, and obesity</td>
</tr>
<tr>
<td>Vitamin B12</td>
<td>Anemia, osteoporosis, sarcopenia, and NAFLD</td>
</tr>
<tr>
<td>Vitamin C</td>
<td>Obesity</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>Vascular function, osteoporosis, and sarcopenia</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>Sarcopenia</td>
</tr>
<tr>
<td>Vitamin K</td>
<td>Osteoporosis, CVD, and diabetes mellitus</td>
</tr>
<tr>
<td>Cr</td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Cu</td>
<td>Anemia, COPD, and osteoporosis</td>
</tr>
<tr>
<td>Mg</td>
<td>Osteoporosis, diabetes complications, diabetes mellitus, prediabetes, and asthma</td>
</tr>
<tr>
<td>Se</td>
<td>Prediabetes, asthma, CVD, and obesity</td>
</tr>
<tr>
<td>Zn</td>
<td>Prediabetes, obesity, and osteoporosis</td>
</tr>
</tbody>
</table>

Disease states leading to micronutrient deficiency

<table>
<thead>
<tr>
<th>Disease</th>
<th>Vitamin deficiency</th>
<th>Mineral deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcoholism</td>
<td>B1, B2, B6, B9, B12, C, D</td>
<td>Zn</td>
</tr>
<tr>
<td>Chronic intestinal failure</td>
<td>A, B12, D, E</td>
<td>Mg, Fe, Zn</td>
</tr>
<tr>
<td>Chronic atrophic gastritis</td>
<td>B12, C, D</td>
<td>Ca, Fe</td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>B vitamins, C, D</td>
<td>Cu</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td>B1, B6, B9, B12, D, K</td>
<td>Fe, Se, Zn</td>
</tr>
<tr>
<td>Liver disease</td>
<td>B1, B6, B9, D, E</td>
<td>Cu, Zn</td>
</tr>
</tbody>
</table>

COPD, chronic obstructive pulmonary disease; NAFLD, nonalcoholic fatty liver disease

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**Table 3: Drugs and specific treatment procedures that lead to micronutrient deficiencies**

<table>
<thead>
<tr>
<th>Drug/treatment</th>
<th>Micronutrient deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRRT</td>
<td>Copper, selenium, vitamin C, folate, thiamine, and carnitine</td>
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<td>Proton pump inhibitors</td>
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<td>Zinc, magnesium</td>
</tr>
<tr>
<td>Glucocorticoids</td>
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</tr>
<tr>
<td>Isoniazid</td>
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</tr>
<tr>
<td>Valproic acid</td>
<td>Carnitine</td>
</tr>
<tr>
<td>Methotrexate, pentamidine, sulfasalazine, phenytoin, cholestyramine</td>
<td>Folate</td>
</tr>
<tr>
<td>Statins</td>
<td>Coenzyme Q10</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>Zinc</td>
</tr>
</tbody>
</table>

ACE, angiotensin-converting enzyme; CRRT, continuous renal replacement therapy
therapy, drug–drug interactions, and disease physiology. Drugs impact nutrient levels in the body through impaired nutrient digestion, increased intestinal and/or urinary losses, decreased bioavailability, decreased storage, and impaired metabolism. Additionally, renal replacement therapy (RRT) has been recognized as a cause for the loss of water-soluble vitamins, especially in the case of continuous RRT (CRRT) that lasts over 7–10 days.

**CURRENT PROFILE OF PUBLIC HEALTH INITIATIVES IN INDIA**

The Prime Minister’s Overarching Scheme for Holistic Nourishment (POSHAN) Abhiyaan is a multiministerial effort to address malnutrition by strengthening and converging actions to support nutrition. It supports several nutrition initiatives and policies to address micronutrient deficiencies, for example, the promotion of early initiation of breastfeeding, immunization, control of childhood illness, iron and folic acid supplementation, adolescent nutrition, etc.

The National Iodine Deficiency Disorders Control Programme surveys the magnitude of iodine deficiency at the district level, supplies iodized salt in place of common salt and then reassesses the magnitude of iodine deficiency after 5 years. The Intensified National Iron Plus Initiative provides prophylactic iron and folic acid supplementation to six target age-groups—under five children, children 5–9 years, adolescent girls and boys, pregnant and lactating mothers, and women of reproductive age-group.

**Table 4:** Recommended dietary allowance for adult men aged >18 years (as per ICMR-NIN 2023)

<table>
<thead>
<tr>
<th>Micronutrient</th>
<th>Sedentary work</th>
<th>Moderate work</th>
<th>Heavy work</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin A (µg/day)</td>
<td>460</td>
<td>460</td>
<td>460</td>
</tr>
<tr>
<td>Thiamine (mg/day)</td>
<td>1.4</td>
<td>1.8</td>
<td>2.3</td>
</tr>
<tr>
<td>Riboflavin (mg/day)</td>
<td>2.0</td>
<td>2.5</td>
<td>3.2</td>
</tr>
<tr>
<td>Niacin (mg/day)</td>
<td>14</td>
<td>18</td>
<td>23</td>
</tr>
<tr>
<td>Pyridoxine (mg/day)</td>
<td>1.9</td>
<td>2.4</td>
<td>3.1</td>
</tr>
<tr>
<td>Folate (µg/day)</td>
<td>300</td>
<td>300</td>
<td>300</td>
</tr>
<tr>
<td>Vitamin B₁₂ (mg/day)</td>
<td>2.2</td>
<td>2.2</td>
<td>2.2</td>
</tr>
<tr>
<td>Ascorbic acid (mg/day)</td>
<td>80</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>Vitamin D (IU/day)</td>
<td>600</td>
<td>600</td>
<td>600</td>
</tr>
<tr>
<td>Magnesium (mg/day)</td>
<td>440</td>
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<td>440</td>
</tr>
<tr>
<td>Zinc (mg/day)</td>
<td>17</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>Iron (mg/day)</td>
<td>19</td>
<td>19</td>
<td>19</td>
</tr>
<tr>
<td>Iodine (µg/day)</td>
<td>140</td>
<td>140</td>
<td>140</td>
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</tbody>
</table>

**Table 5:** Recommended dietary allowance for nonpregnant and nonlactating women aged >18–<60 years, and for pregnant and lactating women (as per ICMR-NIN 2023)

<table>
<thead>
<tr>
<th>Micronutrient</th>
<th>Nonpregnant and nonlactating women aged &gt;18–&lt;60 years</th>
<th>Pregnant and lactating women</th>
<th>Sedentary work</th>
<th>Moderate work</th>
<th>Heavy work</th>
<th>Pregnant</th>
<th>Lactating 0–6 months</th>
<th>Lactating 6–12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin A (µg/day)</td>
<td>1,000</td>
<td>840</td>
<td>1,000</td>
<td>1,000</td>
<td>900</td>
<td>950</td>
<td>950</td>
<td>950</td>
</tr>
<tr>
<td>Thiamine (mg/day)</td>
<td>1.4</td>
<td>1.4</td>
<td>1.7</td>
<td>2.2</td>
<td>2.0</td>
<td>2.1</td>
<td>2.1</td>
<td>2.1</td>
</tr>
<tr>
<td>Riboflavin (mg/day)</td>
<td>1.9</td>
<td>1.9</td>
<td>2.4</td>
<td>3.1</td>
<td>2.7</td>
<td>3.0</td>
<td>2.9</td>
<td>2.9</td>
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<tr>
<td>Niacin equivalent (mg/day)</td>
<td>11</td>
<td>11</td>
<td>14</td>
<td>18</td>
<td>13</td>
<td>16</td>
<td>16</td>
<td>16</td>
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<tr>
<td>Pyridoxine (mg/day)</td>
<td>1.9</td>
<td>1.9</td>
<td>1.9</td>
<td>2.4</td>
<td>2.3</td>
<td>2.16</td>
<td>2.07</td>
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<tr>
<td>Folate (µg/day)</td>
<td>220</td>
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<td>220</td>
<td>220</td>
<td>570</td>
<td>330</td>
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<tr>
<td>Vitamin B₁₂ (mg/day)</td>
<td>2.2</td>
<td>2.2</td>
<td>2.2</td>
<td>2.2</td>
<td>2.45</td>
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<td>Ascorbic acid (mg/day)</td>
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<td>65</td>
<td>80</td>
<td>115</td>
<td>115</td>
<td>115</td>
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<tr>
<td>Vitamin D (IU/day)</td>
<td>600</td>
<td>600</td>
<td>600</td>
<td>600</td>
<td>600</td>
<td>600</td>
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<td>Magnesium (mg/day)</td>
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<td>370</td>
<td>440</td>
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<td>400</td>
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<tr>
<td>Zinc (mg/day)</td>
<td>13.2</td>
<td>13.2</td>
<td>13.2</td>
<td>13.2</td>
<td>14.5</td>
<td>14.1</td>
<td>14.1</td>
<td>14.1</td>
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<tr>
<td>Iron (mg/day)</td>
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<td>29</td>
<td>27</td>
<td>23</td>
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<tr>
<td>Iodine (µg/day)</td>
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<td>140</td>
<td>140</td>
<td>220</td>
<td>280</td>
<td>280</td>
<td>280</td>
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</table>

**Table 6:** Recommended dietary allowance for elderly individuals aged >60 years (as per ICMR-NIN 2023)

<table>
<thead>
<tr>
<th>Micronutrient</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin A (µg/day)</td>
<td>1,000</td>
<td>840</td>
</tr>
<tr>
<td>Thiamine (mg/day)</td>
<td>1.4</td>
<td>1.4</td>
</tr>
<tr>
<td>Riboflavin (mg/day)</td>
<td>2.0</td>
<td>1.9</td>
</tr>
<tr>
<td>Niacin equivalent (mg/day)</td>
<td>14</td>
<td>11</td>
</tr>
<tr>
<td>Pyridoxine (mg/day)</td>
<td>1.9</td>
<td>1.9</td>
</tr>
<tr>
<td>Folate (µg/day)</td>
<td>300</td>
<td>200</td>
</tr>
<tr>
<td>Vitamin B₁₂ (mg/day)</td>
<td>2.2</td>
<td>2.2</td>
</tr>
<tr>
<td>Ascorbic acid (mg/day)</td>
<td>80</td>
<td>65</td>
</tr>
<tr>
<td>Vitamin D (IU/day)</td>
<td>800</td>
<td>800</td>
</tr>
<tr>
<td>Magnesium (mg/day)</td>
<td>440</td>
<td>370</td>
</tr>
<tr>
<td>Zinc (mg/day)</td>
<td>17</td>
<td>13.2</td>
</tr>
<tr>
<td>Iron (mg/day)</td>
<td>19</td>
<td>19</td>
</tr>
<tr>
<td>Iodine (µg/day)</td>
<td>140</td>
<td>140</td>
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Fortifying Micronutrient Supplementation in India

Efficacy of Micronutrient Supplementation in India

There are several studies evaluating the impact of micronutrient supplementation on various populations in India, including adults, children, pregnant women, and those with specific chronic and acute diseases, etc.

Adult nonpregnant, lacto-vegetarian women receiving vitamin B<sub>12</sub> 500 μg daily along with green leafy vegetables demonstrated an increase in serum levels of vitamin B<sub>12</sub> within 2 weeks and a decrease in total homocysteine concentrations. This improvement was not reported for women receiving only green leafy vegetables.

In a study of 75 individuals with T2DM receiving vitamin B<sub>12</sub> and folate [alone or in combination, in addition to the standard oral antidiabetic drug (OAD)] for 8 weeks, an improvement in HbA1c was noted compared with patients receiving only OAD. A clinically meaningful decline in HbA1c (0.5%) was noted for 68 and 79% of patients receiving vitamin B<sub>12</sub> and vitamin B<sub>12</sub> plus folate, respectively, compared with 42% of patients receiving only OAD. Glycemic control was associated with improved insulin sensitivity and increased serum adiponectin levels.

Among vitamin D-deficient T2DM patients with simvastatin-induced impaired exercise performance, vitamin D (60,000 IU once-weekly for 12 weeks) increased skeletal muscle mitochondrial content from 3.6 to 12.1% and increased skeletal muscle citrate synthase activity by 16.7%. Adults with prediabetes and insufficient vitamin D also benefit from supplementation (60,000 IU weekly for 8 weeks followed by 60,000 IU monthly along with 1,250 mg of calcium carbonate), with higher levels of serum vitamin D, lower FPG, postprandial glucose (PPG), tumor necrosis factor α (TNF-α), and interleukin-6 (IL-6) compared with prediabetic vitamin D-deficient individuals receiving only calcium carbonate. Vitamin D supplementation also reduced the rate of progression to diabetes (10.9% vs 26.5%) and increased the rate of reversion to normoglycemia (41.8% vs 20.4%) compared with calcium carbonate supplementation.

Patients with T2DM who received vitamins B<sub>1</sub>, B<sub>6</sub>, B<sub>12</sub>, and E for 5 years had a slower rate of the development of diabetic retinopathy and improved levels of reactive oxygen species (ROS), superoxide dismutase, and malondialdehyde (MDA). In addition, levels of advanced glycation end (AGE) products and vascular endothelial growth factor (VEGF) also improved.

Vitamin C supplementation improves cognition in postmenopausal women, resulting in significantly improved delayed verbal recall, naming, and repetition scores after 12 weeks and a significant decrease in β-amyloid levels. Vitamin C plays a role in improving lung function in healthy adults aged over 35 years, which could be related to the antioxidant potential that could protect against pulmonary diseases. Almost 6 weeks of vitamin C supplementation (250 mg daily) led to an improvement in peak expiratory flow (PEF) and percent-predicted PEF.

Vitamin C, in combination with collagen type II and glucosamine, is beneficial among adults with tendinopathies. About 6 months of supplementation with the combination led to a reduction in mean visual analog scale (VAS) scores compared with patients in the placebo group. Supplementation of vitamins C and E along with exercise leads to an improvement of lipid profile among young Indian males. There was suppression of hemolysis and an improvement in inflammatory markers and lipid parameters.

Efficacy of Multivitamin-mineral Supplementation Role of Micronutrients in Healthy Aging

Micronutrient deficiency is an established cause of reduced cognition, especially among elderly individuals. Deficiencies of vitamins B<sub>1</sub>, B<sub>6</sub>, and C, calcium, magnesium, and zinc lead to a decrease in short-term memory, confusion, visual difficulties, disorientation, and loss of concentration, among various other impacts.

A proprietary multivitamin-mineral (MVM) supplement has been evaluated for its impact on cognitive function in older adults (vs cocoa extract supplement). Daily use of the MVM significantly improved global cognition, particularly in patients with a history of cardiovascular disease (CVD) for up to 2 years. Improvement of executive function and memory was also noted with the use of MVM. The COcoa Supplement and Multivitamin Outcomes Study Web (COSMOS-Web) ancillary study reported that daily MVM supplementation improved the Modified Rey Auditory Verbal Learning Test (ModRey) immediate recall memory from 7.1 to 7.81 after 1-year, and the effect was sustained for over 3 years.

In the COSMOS for the Mind (COSMOS-Mind) study, daily MVM supplementation slowed the decline of incidents of mild cognitive impairment.

The Age-related Eye Disease Study (AREDS) assessed the impact of MVM supplementation on the development and progression of opacities of the lens among adult participants. MVM supplementation led to a 16% reduction in any lens opacities (median follow-up, 6.3 years) and a 25% reduction in nuclear opacity events, which is in line with the findings of the Linxian Cataract Study, which demonstrated a 36% reduction in the prevalence of nuclear cataracts after 5–6 years of treatment.

Multivitamin-mineral Supplementation and Cancer

The role of MVM supplementation in the prevention of chronic disease has been widely debated, with evidence ranging from protective action to possible harm. The Physicians’ Health Study II evaluated the impact of MVM supplementation on the incidence of cancer (excluding nonmelanoma skin cancer) among over 14,000 male physicians. After a mean follow-up of 11.2 years, there was an 8% reduction in the incidence of total cancer in the MVM group compared with the placebo group and an 18% reduction in the incidence of total cancer among men aged 70 years and over. The impact was stronger for secondary prevention of cancer among participants with a history of cancer at baseline compared with participants with no history of cancer.

Multivitamin-mineral Supplementation and Fertility

Oxidative stress is a major cause of male infertility, with antioxidants proposed to be a treatment option. Studies have demonstrated an improvement in semen parameters such as diminished DNA damage, as well as improved antioxidant potential, sperm count, and sperm motility. A recent study compared the effect of antioxidant coenzyme Q10 with the MVM supplement on semen parameters of 130 men with idiopathic oligoasthenospermia. Both treatment groups had improved sperm concentration, progressive motility, total motility, antioxidant capacity, and sperm DNA fragmentation (SDF). However, the MVM supplement scored over coenzyme Q10 for sperm motility, antioxidant capacity, and SDF.
Potential Side Effects and Risks Associated with Supplementation with Higher Doses

Dietary supplements are commonly consumed across the world, both on prescription and over-the-counter. When used for the treatment of deficiency states, vitamin and mineral supplements are well-tolerated since dosing is derived from clinical research. Adverse effects occur due to long-term use, drug–drug interactions, and drug–disease interactions. There is a fallacy among consumers that vitamin supplements are safe. Water-soluble vitamins such as vitamin B<sub>6</sub> can cause neurotoxicity and photosensitivity at doses over 500 mg/day, while elderly patients may experience pyridoxine-associated chronic sensory polyneuropathy. Moderate-to-high doses of vitamin B<sub>6</sub> are associated with peripheral vasodilation, and vasodilation in the eye can cause reversible toxic cystoid macular edema.

Vitamin E at doses over 400 IU/day can cause an increase in all-cause mortality. Doses of 800–1200 mg/day can result in bleeding, and doses above 1200 mg/day can result in diarrhea, weakness, blurred vision, and gonadal dysfunction. The Heart Outcomes Prevention Evaluation (HOPE) reported that patients with vascular disease or diabetes mellitus who received vitamin E 400 IU daily for 7 years had a 13% higher risk of heart failure and a 21% higher risk of hospitalization for heart failure compared to those who did not receive supplementation.

Excess consumption of vitamin A (25,000 IU/day) during pregnancy can lead to birth defects, while children can suffer adverse effects at doses of 1,500 IU/kg/day. Vitamin A can alter bone metabolism and can cause hypercalcemia, profound weight loss, and liver disease. An increased risk of hip fractures and osteoporotic hip fractures has been reported among postmenopausal women who consumed vitamin A supplements for 18 years.

In conclusion, formulations of vitamin/mineral supplements must contain the appropriate balance of micronutrients and should provide micronutrients within the RDA recommended for the Indian population, as per Indian guidelines. Commercially available formulations provide a comprehensive blend of vitamins and minerals, along with botanicals, to meet the specific needs of specific populations with micronutrients within RDA levels that are generally considered safe for long-term use. Vitamins and minerals at high doses can be considered drugs, and therefore, regular monitoring through blood profiling is necessary to ensure the safety of the prescribed treatment in patients who are prescribed therapeutic doses of vitamins.

Specialty Nutrients

Boswellia Extract

Boswellia serrata, which has been used in traditional medicine, contains boswellic acid, which has significant anti-inflammatory activity. 3-acetyl-11-keto-beta-boswellic acid (AKBA) exhibits the strongest inhibitory action on 5-lipoxygenase (5-LOX), and acts synergistically with β-boswellic acid. Patients with osteoarthritis (OA) who receive oral Boswellia serrata extract (BSE) have improved pain and stiffness after 120 days of treatment. An improved knee joint gap and reduced serum levels of high-sensitivity C-reactive protein (hsCRP) are also reported. BSE treatment reduces pain, Western Ontario and McMaster Universities Arthritis Index (WOMAC) pain, and WOMAC stiffness and improves joint function.

Grape Seed Extract

Grape seed extract (GSE) contains several biologically active components that display antioxidant, antiinflammatory, antiapoptotic, antinecrotic, and cardioprotective effects. The cardioprotective effect has been demonstrated through antiatherogenic effects among patients with asymptomatic carotid plaques or abnormal carotid intima-media thickness (CIMT) in a placebo-controlled study (mean maximum CIMT, −5.8%; plaque score, −33.1%) after 24 months, and a lower incidence rate of transient ischemic attack (27.27 vs 28.21%) and rehospitalization for unstable angina (36.36 vs 43.59%).

Hyaluronic Acid

Hyaluronic acid (HA), a naturally occurring mucopolysaccharide, is abundant in the extracellular matrix and pericellular matrix. It contributes to the elastoviscosity of the joint synovial fluid and facilitates the lubrication of joints and muscles. HA at a dose of 60 mg daily for 4 months reduces pain and improves step-up and step-down function in patients with knee OA and synovitis. A dose of 200 mg daily for 8 weeks significantly improves total WOMAC score in patients with knee OA.

Pomegranate Extract

Pomegranate peel extract (PPE) is rich in phenolic compounds which exhibit antioxidative, antitumor, antiinflammatory, neuroprotective, antiviral, and antibacterial activities. Oral administration of fermented pomegranate extracts for 8 weeks reduces oxidative stress and improves moisture, brightness, elasticity, and collagen density of the skin. Obese and overweight individuals who consume pomegranate extract for 30 days have a significant reduction in serum glucose, insulin, total cholesterol, and low-density lipoprotein cholesterol and a significant increase in plasma malondialdehyde (MDA), IL-6, and hs-CRP. Patients with NAFLD who are administered pomegranate extract for 12 weeks have improved liver function, reduced IL-6 levels, and increased total antioxidant capacity (TAC).

Omega-3 Fatty Acids

Eicosapentaenoic (EPA) and docosahexaenoic (DHA) acids are omega-3 fatty acids that have beneficial effects on the cardiovascular system by increasing mitochondria β-oxidation and exerting antiarrhythmic and anti thrombotic effects. Omega-3 fatty acids improve endothelial and vasomotor function and lower blood pressure. Omega-3 fatty acid supplementation reduces the risk of CV mortality by 7%, nonfatal myocardial infarction (MI) by 13%, coronary heart disease events by 9%, major adverse cardiovascular events (MACE) by 5%, and revascularization by 9%.

Biotin

Biotin is a cofactor for carboxylases that are required for the synthesis of keratin, thus contributing to the growth of hair and nails. Low biotin levels are reported in 38% of women experiencing hair loss. Among patients with telogen effluvium who received biotin supplementation for 3 months, 51.5% demonstrated improved hair growth. This was particularly evident for individuals who had deficient serum biotin levels before supplementation. Biotin supplementation also improves hair health in children with uncombable hair.

Prebiotics and Probiotics

Prebiotics are nondigestible, fermentable food ingredients, predominantly fibers that stimulate the growth of gut microorganisms (such as lactobacilli and bifidobacteria). Probiotics are “live microorganisms which, when administered in adequate amounts, confer a health benefit to the host” that inhibit the colonization of the intestine by pathogenic bacteria and enhance the intestinal barrier to improve the immune function of the host. The gut microbiome plays a role in intrinsic primary afferent neuron excitability and modulates the release of biologically active peptides from enterocortic cells. This can
influence mood, blood pressure, sleep cycle, etc. Metabolites of the gut microbiome have immunomodulatory functions, stimulate the autonomic nervous system, and regulate brain development by influencing the homeostasis of microglia. Adults aged 18–60 years with irritable bowel syndrome (IBS), when treated with Bacillus, coagulant Unique IS2 along with standard care, experience a significant reduction in bloating, vomiting, diarrhea, abdominal pain, and stool frequency.

Melatonin
Melatonin (5 methoxy-N-acetyl tryptamine) is a hormone secreted by the pineal gland primarily after sundown. Peak melatonin levels are achieved between 2 and 4 AM, and serum concentrations at night are typically 80 and 120 pg/mL (vs 10–20 pg/mL during the day). Melatonin is a crucial regulator of the sleep-wake cycle. Middle-aged patients with insomnia who receive melatonin for 4 weeks have improved total sleep time, percentage of rapid eye movement, and early morning wake time. Among nonsmoking, nonpregnant, shift-worker female nurses, melatonin significantly decreased sleep onset latency and increased sleep quality compared with placebo. Melatonin supplementation reduces daytime sleepiness among night shift workers and increases sleep duration by up to 20 minutes per day.

L-theanine
L-theanine (γ-glutamylethylamide) has a structure that resembles L-glutamic acid and is isolated from green tea (Camellia sinensis). It acts on glutamate receptors and may have a partial coagonistic effect on the N-methyl-D-aspartate receptor. L-theanine exerts neuroprotective effects that improve sleep quality and reduce cognitive abnormalities, which may occur due to the release of glutathione from astrocytes. A synergistic effect with γ-amino butyric acid (GABA) could improve sleep quality and duration. Supplementation with L-theanine decreases stress-related symptoms, including depression, anxiety traits, and sleep disturbances, along with a significant reduction in the use of sleep medication. Cognitive function, including verbal fluency and executive function, improved after 4 weeks of L-theanine administration.

Collagen: Undenatured Collagen II
The dominant collagen present in articular cartilage is type II collagen. Supplementation of type II collagen may prevent progressive damage to cartilage and aid in the healing of cartilage among patients with OA. Oral tolerance to antigens, amelioration of the T cell-mediated attack on articular cartilage, and suppression of IL-17 associated receptor activator of nuclear factor kappa B ligand (RANKL) expression of clusters of differentiation 4+ T cells is achieved in response to oral supplementation with undenatured type II collagen (UC II). Among Indian patients with OA, UC II intake is associated with a reduction in pain, stiffness, and improved functional mobility, which can improve the quality of life. It reduces WOMAC pain by 95.5%, WOMAC stiffness by 60%, and WOMAC physical function by 80%.

Gingko Biloba
Gingko biloba (G. biloba) contains bioactive terpenoids, flavonoids, polyphenols, and organic acids, which have antiinflammatory, antioxidative, and antiapoptotic effects. Beneficial effects of G. biloba include improvement in memory, cognition, hypertension, dyslipidemia, insulin resistance, and cardiovascular disorders. It also improves mood and quality of life and decreases stress. Thus, G. biloba has a wide range of beneficial effects that could impact several chronic conditions associated with aging.

Addressing Micronutrient Deficiencies in India: Expert Consensus
There is a need to ensure that recommended levels of micronutrients are maintained in all individuals, especially those who are at risk of developing diseases due to deficiency states. Micronutrient supplementation is also essential as supportive therapy for acute and chronic diseases, as well as during recovery and healing. There is a need to focus on risk groups such as children aged <5 years, individuals in lower socioeconomic strata who lack food security, women of the reproductive age-group, pregnant women, and elderly individuals. Each of these groups may have a specific requirement for a micronutrient or a combination of micronutrients, and therapy should be tailored to suit the target group.

The need for nutrient supplementation does not take away from the importance of a well-balanced diet as the foundation for good health and nutrition. However, it is essential to recognize that gaps in nutrition may require supplementation to ensure that the correct balance of nutrients is provided. These micronutrient supplements can also compensate for dietary practices that are inadequate in terms of vital nutrients.

Balancing Nutrient Intake Through Diet
Micronutrient deficiencies typically arise from diets lacking diversity in food groups or from disease to infections. Long-term food-based strategies can effectively prevent these deficiencies sustainably for most of the population. Commercially cultivated cereal, pulse, and oilseed varieties often lack vital nutrients due to nutrient-poor soils or the crops themselves. Unfortunately, these major food crops do not provide the essential micronutrients for normal human growth. To combat nutritional deficiencies, identifying genes and quantitative trait loci related to essential nutrients and integrating these into elite breeding lines may be helpful.

Micronutrient intakes vary significantly between diet inadequacy, Indian dietary patterns, losses due to food processing/cooking, and food impurities (Table 7).22

Do Traditional Indian Diets Meet the Guideline Requirements?
Traditional dietary practices, including the “Thali” (plate) concept, emphasize combinations (grains, lentils, vegetables, dairy, spices, prebiotics and probiotics, and fats) that are local and seasonal. These practices ensure that all the necessary food groups are provided and comply with evidence-based recommendations. Techniques for the preparation, cooking, and preservation of food impact the glycemic index (GI) and nutrient availability. A few traditional ways to lower GI and improve the nutritional value of meals include:

Table 7: Causes of inadequate micronutrient intake via poor diets

<table>
<thead>
<tr>
<th>Causes</th>
<th>Causative features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily diet inadequacy</td>
<td>Vegetarian diets may lack essential omega-3 fatty acids, vitamin B12, and minerals due to reduced bioavailability in plant sources</td>
</tr>
<tr>
<td></td>
<td>Inadequate consumption due to weight-reduction diets, dietary imbalances, and unhealthy eating habits</td>
</tr>
<tr>
<td></td>
<td>Increased consumption of junk food leads to unhealthy snacking habits, eating disorders, emotional and/or physiological stress</td>
</tr>
<tr>
<td>Micronutrient loss in food</td>
<td>Farming techniques and food processing results in plant micronutrient loss</td>
</tr>
<tr>
<td></td>
<td>Cooking leads to a loss of vitamins (25–40%)</td>
</tr>
</tbody>
</table>
- Use whole grains (unpolished, coarse, long grain, and aged).
- Include slow-digesting carbs with high amylose and soluble fiber (e.g., pulses and barley).
- Combine meals with protein, fiber, and healthy fats.
- Opt for resistant-starch-rich foods and preparation methods.
- Use acidic ingredients like lemon, vinegar, or tamarind.
- Choose slightly unripe fruits to control GI since the GI increases as the fruit ripens.

**EXPERT CONSENSUS**

**Adults (Men and Nonpregnant/Nonlactating Women)**

- Food group recommendations to meet the estimated average requirements (EAR) of different nutrients for Indian adult men and nonpregnant and nonlactating women are described in Table 8.
- It is essential to make smart food choices from a diverse range of food groups, obtaining all the necessary nutrients in appropriate quantities.
- An individual should incorporate a daily intake of a minimum of 300 gm of vegetables (50 gm of green leafy vegetables, 200 gm of other vegetables, and 50 gm of roots and tubers). It is advisable to regularly consume 100 gm of fresh fruits.
- High-calorie vegetables and fruits are to be restricted for overweight/obese subjects.
- Adults leading a sedentary lifestyle should aim for around 25 gm of visible fat in their diet, whereas those engaged in strenuous physical work may need 30–40 gm of visible fat.
- Limit salt intake to 6 gm per day.

For effective removal of pesticide residues from food products, follow these methods:
- Wash: Use cold water or a 2% saltwater solution
- Blanch: Briefly treat prewashed vegetables in hot water or steam
- Peel: Remove surface pesticides by peeling fruits and vegetables
- Cook: Use methods like pressure cooking, frying, and baking for animal products. Boil milk at high temperatures to destroy persistent residues.

**Elderly Individuals (Age >65 Years)**

- It is recommended to limit daily oil intake to 20 gm and to avoid the use of butter, vanaspati, and coconut oil.
- Consumption of protein-rich foods like pulses, toned milk, egg whites, and nutrient-rich options containing calcium, micronutrients, and fiber is recommended.
- Besides cereals and pulses, an intake of 200–300 mL of milk and milk products and 400 gm of fruits and vegetables daily for fiber, micronutrients, and antioxidants is suggested.

**MICRONUTRIENT SUPPLEMENTATION**

**Expert Consensus**

Adults (men and nonpregnant/nonlactating women) aged 18–65 years and elderly individuals aged >65 years:

- In adult men and nonpregnant/nonlactating women, if micronutrient deficiencies persist despite adequate dietary interventions, a combination of vitamins and minerals is recommended for men and nonpregnant/nonlactating women aged 18–65 years old.
- A combination MVM is recommended to be taken daily.
- The combination pill should contain essential vitamins, including vitamins A, D, E, and B (B₂, B₆, B₉, B₁₂), and vitamin C and minerals, including copper, selenium, zinc, and magnesium in the correct proportions based on established RDA according to Indian standards.
- Regular monitoring through blood profiling is necessary to ensure the safety of the prescribed treatment in individuals who are prescribed therapeutic doses of vitamins.

**COMMUNITY AWARENESS AND HEALTHCARE PRACTITIONERS ON MICRONUTRIENT SUPPLEMENTATION**

**Expert Consensus**

- Healthcare practitioners (HCPs) should advocate the importance of MVM to various risk groups (children, elderly, obese, those with chronic disease, postsurgical patients, and postillness) and, subsequently, to all patients based on their individual needs.
- Healthcare practitioners (HCPs) should make it a routine to inquire regarding adherence to MVM among all patients during consultation, regardless of indication. This would serve as a reminder to patients.
- Awareness camps can be conducted for specific deficiencies such as iron, folate, vitamin D, and vitamin B₁₂. Screening for these deficiencies at such awareness camps would identify persons who require supplementation.

**FUNDING**

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**CONFLICT OF INTEREST**

Dr Atul Sharma is on Haleon India’s payroll.

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