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Original Article

Drug-Induced Nutrient Depletion

Yogeshwari Gulave*, Ashwini Aher, Namrata Turakane, Sohel Sugavawale

Under The Department Of Pharmacy, SND College Of Pharmacy, Yeola, Nashik, Maharashtra, India

ABSTRACT

Drug-induced nutrient depletion is an increasingly recognized yet often overlooked consequence of long-term pharmacotherapy. Many commonly prescribed medications can interfere with the absorption, metabolism, transport, storage, or excretion of essential vitamins and minerals, resulting in subclinical or clinically significant nutrient deficiencies. These deficiencies may develop gradually over months or years and can contribute to fatigue, anemia, neuropathy, impaired immunity, osteoporosis, poor wound healing, and reduced therapeutic response. Older adults, patients with chronic diseases, individuals receiving polypharmacy, and those with poor nutritional status are particularly vulnerable to these interactions. The relationship between medications and nutritional status is bidirectional, as malnutrition can also alter drug pharmacokinetics and pharmacodynamics, thereby influencing treatment outcomes. This review summarizes the current evidence regarding drug-induced nutrient depletion associated with commonly used therapeutic classes, including proton pump inhibitors, metformin, diuretics, antiepileptics, statins, oral contraceptives, corticosteroids, and antibiotics. The underlying mechanisms, clinical manifestations, risk factors, diagnostic considerations, prevention strategies, and appropriate nutritional interventions are discussed. Although evidence supporting some drug–nutrient interactions is well established, many interactions require further high-quality clinical research to determine their true clinical significance. Early recognition of patients at risk, regular nutritional assessment, appropriate dietary counselling , and targeted supplementation when indicated may help prevent nutrient deficiencies, improve medication safety, and enhance overall patient outcomes. Increased awareness among healthcare professionals regarding drug-induced nutrient depletion is essential for optimizing pharmacotherapy and promoting comprehensive patient care.

Keywords: Drug-induced nutrient depletion; Drug–nutrient interactions; Micronutrient deficiency; Vitamins; Minerals; Polypharmacy; Nutritional supplementation; Patient safety.

INTRODUCTION

Importance of micronutrients, including vitamins and minerals, are essential nutrients required in small amounts for normal growth, development, and maintenance of health. They are involved in numerous physiological processes, including energy production, enzyme function, immune regulation, DNA synthesis, antioxidant defense, nerve conduction, bone health, and tissue repair. Although required in minute quantities, an adequate intake of these nutrients is essential for maintaining normal cellular functions and preventing disease. Deficiency or depletion of even a single micronutrient can impair metabolic processes and adversely affect overall health.[1-4]

Drug-induced nutrient depletion (DIND) refers to the reduction in the body's stores of essential vitamins, minerals, or other nutrients caused by the prolonged use of prescription or over-the-counter (OTC) medications. Unlike nutritional deficiency, which primarily results from inadequate dietary intake, DIND occurs when medications interfere with nutrient absorption, metabolism, transport, storage, or excretion. These changes may gradually lead to subclinical or clinically significant deficiencies, particularly during long-term therapy. Drug–nutrient interactions are increasingly recognized as an important aspect of patient care because they can influence both nutritional status and therapeutic outcomes.[1-6]

The increasing prevalence of chronic diseases such as hypertension, diabetes mellitus, cardiovascular diseases, gastrointestinal disorders, depression, and osteoporosis has led to widespread long-term use of

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medications and polypharmacy. Older adults are particularly susceptible to drug-induced nutrient depletion because aging, chronic illness, reduced dietary intake, and multiple drug therapies collectively increase the risk of micronutrient depletion. Since the symptoms are often nonspecific such as fatigue, muscle weakness, anemia, impaired immunity, and cognitive changes they are frequently overlooked or mistaken for disease progression or normal aging. Early recognition and appropriate management of DIND are therefore essential to prevent complications, improve treatment outcomes, and enhance patients' quality of life.[1-6]

2. Drug -induced nutrient depletion : major drug-nutrient interaction

2.1 Vitamin B_{12}

Vitamin B_{12} is a water-soluble vitamin essential for DNA synthesis, normal red blood cell formation, and neurological function. Its absorption is a multistep process. Gastric acid and pepsin facilitate the release of protein-bound vitamin B_{12} from food. The released vitamin B_{12} subsequently binds to intrinsic factor and is absorbed mainly in the terminal ileum. Therefore, drugs that alter gastric acid secretion or interfere with the absorption of the vitamin B_{12}–intrinsic factor complex may contribute to vitamin B_{12} depletion.[4]

2.1.1. Proton Pump Inhibitors and H_2-Receptor Antagonists

Proton pump inhibitors (PPIs) and H_2-receptor antagonists (H_2RAs) reduce gastric acid secretion. Reduced gastric acidity may impair the release of protein-bound vitamin B_{12} from food, thereby decreasing its availability for absorption. Long-term use of these acid-suppressing medications has been associated with lower vitamin B_{12} concentrations and an increased risk of depletion in some individuals; however, evidence from clinical studies is not entirely consistent.[16-18]

The risk may be greater with prolonged treatment and in susceptible populations, particularly older adults and individuals with conditions that already reduce gastric acid secretion, such as Helicobacter pylori infection or atrophic gastritis. Other factors, including drug dose, treatment duration, age, smoking, nutritional status, and individual differences in drug response, may also influence the risk.[15]

The effect of acid-suppressing drugs is primarily related to the absorption of food-bound vitamin B_{12}. Vitamin B_{12} present in supplements and fortified foods is generally less dependent on gastric acid for release. Routine vitamin B_{12} screening is not required for every patient receiving PPI or H_2RA therapy; however, assessment of vitamin B_{12} status may be considered in patients receiving prolonged therapy who have additional risk factor or clinical feature suggestive of deficiency.[14-18]

2.1.2 Metformin

Long-term metformin therapy is associated with reduced serum vitamin B_{12} concentrations and an increased risk of vitamin B_{12} deficiency. Metformin may interfere with the absorption of the vitamin B_{12}–intrinsic factor complex in the terminal ileum. One proposed mechanism involves interference with calcium-dependent uptake of the complex by the ileal cubilin receptor.[10,12]

Additional mechanisms that have been proposed include alterations in intestinal motility, changes in bile acid metabolism, and intestinal bacterial overgrowth. The risk of vitamin B_{12} depletion appears to increase with higher metformin doses and longer treatment duration.[9-13]

Patients receiving prolonged metformin therapy, particularly those with anemia, peripheral neuropathy, or other risk factors for vitamin B_{12} deficiency, may benefit from periodic assessment of vitamin B_{12} status. If deficiency is identified, appropriate vitamin B_{12} supplementation can restore vitamin B_{12} concentrations and may help prevent or limit neurological complications.[9-11]

2.2 Vitamin D

Vitamin D plays an essential role in maintaining calcium and phosphorus homeostasis and supporting normal bone mineralization. Several medications can interfere with vitamin D metabolism or calcium absorption, thereby contributing to reduced vitamin D status and impaired bone health.[19-24]

2.2.1. Corticosteroids:

Long-term corticosteroid therapy is strongly associated with disturbances in calcium and vitamin D metabolism. Glucocorticoids can reduce intestinal and renal calcium absorption and may interfere with the physiological actions of vitamin D. Certain corticosteroids, such as dexamethasone, may also enhance the activity of vitamin D-24-hydroxylase, an enzyme involved in the degradation of vitamin D metabolites. These effects can disturb calcium homeostasis and contribute to reduced bone formation, bone loss, and an increased risk of osteoporosis and fractures. Population-based evidence has also suggested a higher prevalence of vitamin D deficiency among individuals using systemic corticosteroids compared with non-users.[23,24]

2.2.2 Antiepileptic drugs:

Long-term treatment with certain antiepileptic drugs (AEDs), particularly enzyme-inducing agents such as phenytoin, phenobarbital, and carbamazepine, has been associated with reduced vitamin D status. These medications increase hepatic cytochrome P450 enzyme activity, which accelerates the conversion of vitamin D into inactive metabolites. Consequently, prolonged exposure may decrease circulating vitamin D concentrations and impair calcium homeostasis. Clinical studies have reported lower vitamin D concentrations and reduced bone mineral density among chronic AED users compared with individuals not receiving these medications. Phenytoin use has also been associated with an increased risk of fractures. Vitamin D deficiency has also been reported in pediatric patients receiving long-term AED therapy, further highlighting the potential importance of monitoring vitamin D status in patients receiving chronic treatment.[19]

2.3 Vitamin B6 (Pyridoxine) Depletion

Vitamin B6 is involved in numerous metabolic processes, including amino acid metabolism, neurotransmitter synthesis, and normal nervous system function. Several medications can interfere with vitamin B6 metabolism, reduce its active form, pyridoxal-5′-phosphate (PLP), or increase its urinary loss, potentially leading to deficiency and neurological complications.[4,6]

2.3.1. Isoniazid

Isoniazid (INH) is an important first-line drug used in the treatment of tuberculosis. It can interfere with vitamin B6 metabolism by binding with pyridoxine and its active metabolites, thereby reducing vitamin B6 availability and increasing its urinary loss. Prolonged treatment may therefore result in pyridoxine deficiency, which can manifest particularly as peripheral neuropathy. Pyridoxine supplementation is commonly used during isoniazid therapy, especially in patients at increased risk of deficiency, such as those with malnutrition, alcohol dependence, diabetes, or chronic kidney disease.[35]

2.3.2. Cycloserine

Cycloserine is a second-line antitubercular drug commonly used for drug-resistant tuberculosis. It can increase urinary loss of pyridoxine and consequently increase the requirement for vitamin B6 during treatment. Reduced vitamin B6 availability may contribute to the neurological and central nervous system toxicity associated with cycloserine, including seizures and peripheral neuropathy. Pyridoxine supplementation is therefore often administered with cycloserine to help reduce these adverse effects.[35]

2.3.3. Antiepileptic Drugs

Certain enzyme-inducing antiepileptic drugs, particularly phenytoin and carbamazepine, can increase the metabolism and breakdown of vitamin B6. Long-term use may result in reduced plasma concentrations of PLP, the biologically active form of vitamin B6. Valproic acid has also been associated with alterations in vitamin B6 status. Reduced vitamin B6 availability may contribute to neurological complications and disturbances in homocysteine metabolism in some patients receiving long-term antiepileptic therapy.[19-21]

2.4 VITAMIN A DEPLETION

Vitamin A is a fat-soluble vitamin that plays an important role in vision, immune function, reproduction, cell differentiation, and maintenance of healthy skin and mucous membranes. Dietary vitamin A is obtained as preformed vitamin A (retinol and retinyl esters) from animal foods and as provitamin A carotenoids, particularly β-carotene, from plant

sources. Its intestinal absorption depends on adequate dietary fat, bile acids, and pancreatic enzymes. Therefore, drugs that interfere with fat digestion or bile acid function may reduce vitamin A absorption and contribute to depletion.[4]

2.4.1. Orlistat

Orlistat is a lipase inhibitor used in the management of obesity. It inhibits gastric and pancreatic lipases, thereby reducing the digestion and absorption of dietary fat. Since vitamin A is a fat-soluble vitamin, this reduction in fat absorption can also decrease its intestinal absorption. Clinical studies have reported modest reductions in serum vitamin A concentrations during long-term orlistat treatment, although vitamin A appears to be less affected than some other fat-soluble vitamins. Therefore, prolonged orlistat therapy may increase the risk of vitamin A depletion, particularly in individuals with inadequate dietary intake. A daily multivitamin containing vitamin A and other fat-soluble vitamins is generally recommended, with administration separated from orlistat by at least 2 hours.[31]

2.4.2. Bile Acid Sequestrants

Bile acid sequestrants, such as cholestyramine, colestipol, and colesevelam, are used primarily to reduce blood cholesterol levels. These drugs bind bile acids in the intestinal lumen and reduce their availability for fat digestion and micelle formation. Because bile acids are required for efficient absorption of fat-soluble vitamins, long-term treatment may reduce the absorption of vitamin A and contribute to subclinical deficiency. Therefore, patients receiving prolonged therapy, particularly those at increased risk of nutritional deficiencies, may require monitoring of fat-soluble vitamin status and appropriate supplementation.[4]

2.5 Vitamin B9 (Folate) Depletion

Folate (vitamin B9) is a water-soluble vitamin essential for DNA and RNA synthesis, cell division, and amino acid metabolism. It also participates in the conversion of homocysteine to methionine. Several medications can interfere with folate metabolism, absorption, or utilization and may consequently contribute to reduced folate status.[4]

2.5.1. Methotrexate

Methotrexate is a folate antagonist widely used in cancer therapy and in the treatment of autoimmune disorders such as rheumatoid arthritis and psoriasis. It structurally resembles folate and inhibits dihydrofolate reductase, thereby reducing the availability of biologically active folate required for nucleotide synthesis. This interference can result in manifestations resembling folate deficiency, including megaloblastic changes and other hematological toxicities. Studies in patients receiving low-dose methotrexate have demonstrated reductions in serum and erythrocyte folate concentrations. Folic acid supplementation is therefore commonly used with low-dose methotrexate to reduce treatment-related toxicity while maintaining therapeutic efficacy.[37-43]

2.5.2. Trimethoprim-Containing Drugs

Trimethoprim inhibits dihydrofolate reductase and interferes with folate metabolism. Although its primary target is bacterial folate metabolism, prolonged or high-dose therapy may also affect human folate metabolism. Clinically significant effects are uncommon at standard therapeutic doses but may include leukopenia or megaloblastic anemia, particularly in individuals who are already folate deficient. Greater caution is therefore required in malnourished patients, older adults, and individuals with malabsorption.[4]

2.5.3. Antiepileptic Drugs

Certain antiepileptic drugs, particularly enzyme-inducing agents such as phenytoin and carbamazepine, have been associated with reduced serum or red blood cell folate concentrations. Increased hepatic enzyme activity may accelerate folate metabolism, while other mechanisms may also contribute to reduced folate availability. Long-term therapy may therefore increase the risk of folate depletion, especially in patients with inadequate dietary folate intake. Monitoring of nutritional status and appropriate folate intake may be beneficial in susceptible individuals.[19-21]

2.6 Vitamin B1 (Thiamine)

Thiamine (vitamin B1) is an essential water-soluble vitamin that plays a major role in energy metabolism, glucose utilization, and normal nervous-system function. Its active form, thiamine pyrophosphate (TPP), acts as a cofactor for several important metabolic enzymes. Since body stores are limited, deficiency can develop with malnutrition, chronic alcohol use, gastrointestinal disorders, bariatric surgery, and prolonged diuretic use. Thiamine deficiency can lead to impaired energy production, neurological dysfunction, beriberi, and Wernicke encephalopathy.[25,29]

2.6.1. Furosemide and Other Loop Diuretics

Furosemide is a loop diuretic widely used in the management of conditions such as heart failure, hypertension, and fluid overload. Prolonged treatment with loop diuretics has been associated with reduced thiamine status. The primary mechanism is thought to be increased urinary excretion of thiamine resulting from sustained diuresis. Studies in both humans and experimental models have demonstrated that thiamine loss in urine increases with urine flow, suggesting that enhanced urinary loss contributes substantially to depletion.

Patients with chronic heart failure receiving loop diuretics have been reported to have a higher prevalence of biochemical thiamine deficiency than individuals without heart failure. The risk appears to increase with higher doses and prolonged treatment with furosemide. This may be particularly important in patients receiving high-dose therapy for several months.[25-27]

Older adults may be especially vulnerable because they are already at greater risk of inadequate dietary thiamine intake. Studies in elderly individuals have demonstrated an association between cumulative furosemide exposure and declining thiamine status during hospitalization. Therefore, prolonged or high-dose loop-diuretic therapy may increase the likelihood of thiamine depletion, particularly in patients with heart failure, poor nutritional intake, or other risk factors for deficiency.[25-27,32]

2.6.2 Fluorouracil (5-FU)

Fluorouracil (5-FU) is an antimetabolite chemotherapeutic agent commonly used in the treatment of several solid tumors, including colorectal and gastric cancers. Treatment with 5-FU has been associated with alterations in thiamine metabolism and reduced thiamine availability.

Increased thiamine utilization or metabolism during 5-FU therapy may contribute to depletion of body thiamine stores. Clinical reports have described serious manifestations of thiamine deficiency, including beriberi and Wernicke encephalopathy, in patients receiving chemotherapy regimens containing 5-FU. These complications highlight the importance of recognizing thiamine deficiency in patients undergoing prolonged or intensive chemotherapy, particularly when nutritional intake is inadequate.[28.29]

3. Classification of Drugs Causing Nutrient Depletion

Drugs can cause nutrient depletion through several mechanisms, including reduced nutrient absorption, increased nutrient excretion, altered nutrient metabolism, and changes in nutrient utilization. Various commonly used medications, such as gastrointestinal drugs, antidiabetic drugs, cardiovascular drugs, and anti-inflammatory agents, may interfere with the availability or metabolism of vitamins and minerals.[1-6]

3.1 Gastrointestinal Acid-Suppressing Drugs

Proton pump inhibitors (PPIs) and H_2-receptor antagonists (H_2 blockers) reduce gastric acid secretion. Long-term use may interfere with the absorption or availability of vitamin B12, magnesium, iron, and calcium.[14-18]

3.2 Bile Acid Sequestrants

Bile acid sequestrants can interfere with the absorption of fat-soluble vitamins, particularly vitamins A, D, E, and K.[2,4]

3.3 Antidiabetic Drugs

Metformin, particularly with long-term use, is associated with reduced vitamin B12 absorption and may contribute to vitamin B12 depletion.[9-13]

3.4 Anti-inflammatory and Corticosteroid Drugs

Long-term use of corticosteroids, such as prednisone, can interfere with calcium and vitamin D metabolism, potentially contributing to reduced bone mineralization and osteoporosis.[22-24]

4.Clinical Considerations and Prevention of Drug-Induced Vitamin Depletion

Drug-induced depletion of vitamins B12, A, D, B9 (folate), B1 (thiamine), and B6 (pyridoxine) may occur through altered intestinal absorption, increased metabolism, impaired utilization, or increased urinary excretion. The clinical importance of these interactions depends on the type and dose of medication, duration of therapy, baseline nutritional status, dietary intake, and individual patient risk factors.[1-6]

Vitamin B12: Long-term use of metformin and acid-suppressing medications such as proton pump inhibitors and H2-receptor antagonists may reduce vitamin B12 availability in susceptible individuals. Patients receiving prolonged therapy, particularly those with additional nutritional risk factors, may benefit from periodic assessment of vitamin B12 status. Adequate dietary intake and supplementation should be considered when deficiency is identified or the risk is high.[9-18]

Vitamin A: Drugs that interfere with fat absorption, particularly orlistat, may reduce the absorption of vitamin A. Patients receiving long-term therapy with such medications should maintain an adequate intake of vitamin A through the diet. Monitoring may be considered in individuals at increased risk of deficiency or those receiving prolonged treatment.[31]

Vitamin D: Corticosteroids and certain antiepileptic drugs may interfere with vitamin D metabolism and contribute to reduced vitamin D status and impaired bone health. Patients receiving long-term therapy, especially those with additional risk factors for bone loss, should receive adequate vitamin D and calcium through diet or supplementation when clinically indicated. Assessment of vitamin D status and bone health may be appropriate in high-risk individuals.[19-24]

Vitamin B9 (Folate): Antifolate drugs such as methotrexate and trimethoprim, as well as sulfasalazine and some enzyme-inducing antiepileptic drugs, may reduce folate availability or interfere with folate metabolism. Patients receiving prolonged treatment should have adequate dietary folate intake, and supplementation may be required according to the medication and clinical condition. Folic acid supplementation is commonly used with low-dose methotrexate to reduce treatment-related toxicity.[36-43]

Vitamin B1 (Thiamine): Certain diuretics, particularly loop diuretics, may increase urinary thiamine loss and contribute to reduced thiamine status during prolonged therapy. Patients receiving long-term diuretic treatment who have poor dietary intake, alcohol-related nutritional risk, or other predisposing factors may require closer nutritional assessment and appropriate thiamine supplementation.[25-27]

Vitamin B6 (Pyridoxine): Some medications, particularly isoniazid and certain antiepileptic drugs, can interfere with vitamin B6 metabolism or increase its utilization. Long-term therapy may therefore increase the risk of pyridoxine deficiency and associated neurological or hematological manifestations. Appropriate dietary intake and supplementation should be considered in patients at increased risk, particularly when preventive supplementation is recommended with specific drug therapies.[2,19-21]

Overall, routine vitamin supplementation is not necessary for every patient receiving these medications. Prevention should be individualized according to the specific drug, duration of treatment, dietary intake, baseline nutritional status, and presence of additional risk factors. Healthcare professionals should identify patients at increased risk, provide appropriate dietary advice, and consider laboratory monitoring or supplementation when clinically justified. Further clinical studies are needed to establish standardized monitoring and prevention strategies for drug-induced vitamin depletion.[1-6]

CONCLUSION

Drug-induced nutrient depletion is an important but frequently underrecognized consequence of long-term pharmacotherapy. Commonly used medications

can influence the absorption, metabolism, utilization, transport, or excretion of essential vitamins and minerals, potentially leading to clinically significant nutritional deficiencies. The evidence discussed in this review highlights important drug–nutrient associations involving vitamin B_{12}, vitamin D, vitamin B_6, vitamin A, folate (B_9), and thiamine (B_1), particularly with medications such as metformin, proton pump inhibitors, H_2-receptor antagonists, corticosteroids, antiepileptic drugs, isoniazid, orlistat, methotrexate, and loop diuretics.[9-35]

The clinical consequences of nutrient depletion can range from nonspecific symptoms such as fatigue and weakness to more serious complications, including anemia, peripheral neuropathy, impaired bone health, neurological dysfunction, and reduced quality of life. The risk is particularly relevant in patients receiving prolonged or high-dose therapy, older adults, individuals with chronic diseases, pat`ients receiving multiple medications, and those with inadequate dietary intake or pre-existing nutritional deficiencies.[5,6]

Prevention and management should therefore focus on identifying patients at increased risk rather than applying routine supplementation to all individuals receiving these medications. Appropriate dietary counselling, assessment of nutritional status, laboratory monitoring when clinically indicated, and targeted supplementation can help prevent or correct deficiencies while allowing necessary pharmacotherapy to continue safely. Healthcare professionals, particularly pharmacists and physicians, have an important role in recognizing potential drug–nutrient interactions and incorporating nutritional considerations into medication management.[1-6]

Overall, greater awareness of drug-induced nutrient depletion can improve medication safety, support better therapeutic outcomes, and promote comprehensive patient care. Further well-designed clinical studies are needed to clarify the clinical significance of individual drug–nutrient interactions and to establish standardized recommendations for screening, monitoring, and supplementation in long-term medication users.[1-6]

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