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Review Article

Drug-Induced Vitamin Deficiency

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ABSTRACT

Drug-induced vitamin depletion can occur in hospitalized patients due to the administration of specific medications, which could potentially adversely affect patient outcomes. Signs and symptoms related to vitamin deficiency while taking certain medications should be monitored carefully and managed appropriately if those deficiencies are clinically significant. This article reviews potential drug-induced vitamin depletion and discusses the evidence supporting vitamin deficiency related to the use of specific medications.

Keywords: Drug-related side effects and adverse reactions; Drug interactions; Vitamins

INTRODUCTION

Vitamins are essential organic substances required in small amounts in our body. Vitamins play an important role in maintaining fundamental cellular functions of the body such as energy production and metabolic processes. Each vitamin has unique biochemical and physiologic activities.

Drug-induced vitamin depletion can occur in hospitalized patients as they are generally administered numerous medications to treat their condition(s), some of which are associated with deficiencies in certain vitamins. Although the mechanisms by which vitamin depletion induced by drugs are complex and not well understood, it is necessary to be aware of potential vitamin depletion associated with medication use.

This article reviews potential drug-induced vitamin depletion and the evidence supporting vitamin deficiency related to the use of specific medications.

VITAMIN A DEPLETION

1. Orlistat

Orlistat is a drug used to treat obesity in conjunction with a low calorie diet. Because orlistat inhibits the absorption of dietary fats by inactivating gastric and pancreatic lipases, the absorption of fat-soluble vitamin A may also be reduced [1]. A previous meta-analysis of 16 clinical trials of orlistat reported that levels of vitamin A were decreased by orlistat treatment [2]. Furthermore, a 4-year randomized controlled trial reported a statistically significant decrease in concentrations of fat-soluble vitamins, including vitamin A, in the orlistat group compared to the placebo group [3]. Therefore, daily intake of multivitamin supplements containing fat-soluble vitamins is recommended at least 2 hours before or after orlistat administration [4].

2. Cholestyramine

Cholestyramine, a bile acid sequestrant, is a cholesterol-lowering agent used to treat dyslipidemia. Cholestyramine lowers cholesterol by inhibiting the absorption of bile acids in the intestine, resulting in conversion of hepatic cholesterol into bile acid [5]. As bile acid plays a critical role in absorbing fat-soluble vitamins, malabsorption of bile acid due to cholestyramine use may lead to vitamin A deficiency. Only a few studies have investigated the clinical effect of vitamin A deficiency induced by bile acid sequestrants [6,7]. Nonetheless, approved product labels support vitamin A supplementation while on cholestyramine for patients susceptible to fat-

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soluble vitamin deficiencies [8].

VITAMIN B1 (THIAMIN) DEPLETION

1. Furosemide

Furosemide is a loop diuretic used to treat heart failure and hypertension. Furosemide has been shown to induce thiamine deficiency [9,10]. Suggested mechanism is the urinary loss of thiamine due to increased urine flow [11]. Other studies have proposed that furosemide can reduce intracellular thiamine levels by decreasing cellular uptake or intestinal absorption of thiamine [12]. Furosemide is known to cause thiamine deficiency in a dose-dependent manner. Patients with heart failure receiving high-dose furosemide (>80 mg/d) for a prolonged duration (>6 months) are at increased risk of thiamine deficiency [13]. The incidence of thiamine deficiency in patients with chronic heart failure is estimated to range from 21%~98% [14].

2. Fluorouracil

Fluorouracil (or 5-fluorouracil, 5-FU) is a chemotherapeutic agent used to treat various solid tumors including colorectal and gastric cancers. Patients receiving 5-FU have increased thiamine metabolism and therefore decreased thiamine levels [15]. Cases of beriberi or Wernicke's encephalopathy, which are neuropsychiatric syndromes caused by thiamine deficiency, have been reported in patients who received chemotherapy including 5-FU [16,17]. It has been proposed that adverse reactions related to 5-FU-induced thiamine deficiency can be reversed by thiamine supplementation [18].

VITAMIN B3 (NIACIN) DEPLETION

1. Isoniazid and pyrazinamide

Isoniazid (INH) and pyrazinamide are medications used to treat tuberculosis. Pellagra, a multi-system disorder caused by niacin deficiency, has been reported in patients receiving INH and/or pyrazinamide. These agents can interfere with the production of endogenous niacin due to the structural similarity between those drugs and vitamin B3 (niacin) [19]. In addition, it has been suggested that INH depletes niacin by inhibiting the intestinal absorption of niacin [20]. Although pellagra is no longer common due to niacin fortification of foods, patients at higher risk may require close monitoring of INH-induced niacin deficiency [21].

VITAMIN B6 (PYRIDOXINE) DEPLETION

1. Isoniazid

INH is a commonly used anti-tuberculotic agent. INH inhibits mycolic acid synthesis, but also interferes with vitamin B6 synthesis, which is the suspected mechanism of INH-induced peripheral neuropathy. INH is thought to form a complex with pyridoxine, and thus increase the excretion of pyridoxine during treatment [22]. Accordingly, daily pyridoxine supplementation (50~100 mg/d) is recommended to prevent INH-associated pyridoxine deficiency [23]. Higher doses of pyridoxine might be required in those at increased risk of developing peripheral neuropathy, patients receiving higher doses of INH, and those with alcohol dependency, malnutrition, diabetes mellitus, or chronic kidney disease [22, 24].

2. Cycloserine

Cycloserine is a broad-spectrum antibiotic used as a second-line therapy in drug-resistant tuberculosis. Dose-related central nervous system toxicity of cycloserine is associated with pyridoxine deficiency [23]. Cycloserine is known to increase the renal excretion of pyridoxin, thereby increasing pyridoxine requirements during therapy [25]. Accordingly, co-administration of cycloserine and pyridoxine (50 mg per 250 mg of cycloserine) is recommended to decrease cycloserine-related neurotoxicity [26].

3. Anti-epileptic drugs

Anti-epileptic drugs (AEDs) are used to treat epileptic seizures. Several AEDs, including phenytoin and carbamazepine, increase the catabolism of vitamin B6 by their hepatic enzyme-inducing effect [27]. Enzyme-inducing antiepileptic drug (EIAED) use is also associated with decreased levels of pyridoxal 5′-phosphate (PLP), a major active derivative of vitamin B6. One study reported that the prevalence of vitamin B6 deficiency in patients treated with EIAED was 48% [28].

4. Levodopa

Levodopa, a precursor of dopamine, is used to treat Parkinson's disease and dopamine-responsive dystonia. Levodopa may cause vitamin B6 deficiency through rapid depletion of PLP. The complex formed between levodopa and PLP can inhibit pyridoxal kinase, an enzyme responsible for pyridoxin activation [23]. Thus, vitamin B6 supplementation should be considered for patients on levodopa therapy [29].

5. Theophylline

Theophylline is used to treat respiratory disorders, including asthma and chronic obstructive pulmonary disease. Theophylline decreases circulating PLP levels by acting as a noncompetitive inhibitor of pyridoxal kinase [23]. This could lead to a decrease in plasma PLP levels and neurological adverse effects, including seizures. One clinical trial showed that patients on theophylline had decreased PLP levels after treatment. In that study, 10 mg pyridoxine was shown to counteract the antagonistic effect of theophylline on vitamin B6 metabolism [30].

VITAMIN B7 (BIOTIN) DEPLETION

1. Anti-epileptic drugs

EIAEDs increase the catabolism of vitamin B7 and the urinary excretion of its metabolites, possibly resulting in vitamin B7 deficiency [31]. Carbamazepine and primidone also contribute to low levels of vitamin B7 by inhibiting the uptake of biotin in the intestine [32]. A previous study reported that patients undergoing long-term anticonvulsant therapy for at least one year had significantly greater urinary excretion of biotin metabolites than the control group. A follow-up study reported similar findings, namely that biotin catabolism was accelerated by antiepileptics, resulting in low levels of vitamin B7 [33,34]. Therefore, supplementation with biotin could help prevent adverse health outcomes related to anticonvulsant-induced biotin deficiency.

2. Lipoic acid

Lipoic acid, also known as thioctic acid, is mainly prescribed for the management of diabetic peripheral neuropathy due to its antioxidant properties [35]. Its cellular uptake across the cell membrane is mediated by sodium-dependent multivitamin transporters (SMVTs), which also transport biotin and pantothenic acid [36]. Since lipoic acid and biotin bind to SMVTs competitively, administration of lipoic acid may decrease the cellular uptake of biotin [37]. Decreased activity of biotin-dependent enzymes in the liver has been reported with chronic administration of lipoic acid. However, it is still unclear whether this mechanism fully explains the adverse pathologic effect of lipoic acid in patients [38]. Biotin supplementation should be considered in patients taking high doses of lipoic acid.

VITAMIN B9 (FOLATE) DEPLETION

1. Antifolate: methotrexate

Methotrexate (MTX) is a folate antagonist used for cancer and autoimmune disease treatment. Methotrexate is a structural analogue of folate and acts as an antimetabolite by blocking the action of folate in DNA synthesis. Antifolate properties of methotrexate explain the similarity of its adverse effects to the signs and symptoms of folate deficiency [39]. A randomized trial of 113 patients with rheumatoid arthritis receiving 48-week MTX treatment fond decreased serum and erythrocyte folate levels in the MTX plus placebo group as opposed to the MTX plus folic acid group [40]. Accordingly, supplementation with folic acid is recommended to prevent MTX-related toxicities, especially in patients taking low-dose methotrexate for rheumatoid arthritis and psoriasis [41].

2. Antifolate: sulfonamides

Trimethoprim-sulfamethoxazole (TMP-SMX) is an antibiotic used to treat infectious diseases. TMP-SMX blocks bacterial biosynthesis of folate, eventually inhibiting bacterial growth. Although uncommon at therapeutic doses, inhibition of folate metabolism by TMP-SMX can cause dose-related leukopenia and megaloblastic anemia. Therefore, TMP-SMX should be given with caution to patients at risk of folate deficiency such as elderly patients, those with malabsorption syndrome, or malnourished patients [42].

Sulfasalazine is a sulfonamide drug with anti-inflammatory properties used to treat ulcerative colitis. Patients taking sulfasalazine can develop folate deficiency as sulfasalazine is known to interfere with intestinal folate absorption. Folate is absorbed mainly through the proton-coupled folate transporter (PCFT), which plays a critical role in folate transport across the membrane of cells lining the proximal small intestine. Sulfasalazine inhibits PCFT-mediated folate transport therefore interferes with the intestinal absorption of folate [43]. Malabsorption of folate due to sulfasalazine can also be explained by inhibition of the enzyme that converts the poly-glutamate forms of tetrahydrofolates into the absorbable form of folate [44]. Therefore, an increase in dietary folate or folate supplementation may be required in patients taking sulfasalazine.

3. Antiepileptic drugs

Studies have suggested that EIAEDs can reduce levels of serum folate [45]. Deficiency of folate, an important cofactor in the metabolism of homocysteine, can occur through induction of hepatic enzymes. Folate supplementation can potentially prevent folate deficiency and cardiovascular events caused by high levels of homocysteine in patients with epilepsy [46].

VITAMIN B12 DEPLETION

1. Proton pump inhibitors & H_2-receptor antagonists

Proton pump inhibitors (PPIs) and H_2-receptor antagonists (H_2RAs) are widely used acid-suppressive agents. Both are approved for various acid-related disorders, including gastroesophageal reflux disease, peptic ulcer disease, and Zollinger-Ellison syndrome. However, these drugs are well-known to reduce serum vitamin B12 levels with prolonged use. Loss of gastric acid due to PPI or H_2RA use inhibits the conversion of pepsinogen to pepsin. As pepsin promotes the release of vitamin B12 from ingested proteins, low levels of gastric acid can consequently lead to malabsorption of vitamin B12 in the body [47].

Several studies have reported an association between long-term use of gastric acid-lowering agents and low serum vitamin B12 levels [48]. A case-control study found that taking a PPI or H_2RA for more than two years was significantly associated with an increased risk of vitamin B12 deficiency (odds ratio 1.65 for PPI, 1.25 for H_2RA, respectively) [49]. Similar results were found in the elderly population using a PPI or H_2RA for more than 12 months [50]. However, further

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randomized controlled trials using multiple biomarkers of vitamin B12 status are needed to confirm these associations [51].

2. Metformin

Metformin is an oral hypoglycemic agent used to treat type 2 diabetes that is known to decrease serum vitamin B12 levels. Vitamin B12 forms a complex with intrinsic factor (IF) before its absorption in the duodenum. Metformin is thought to cause vitamin B12 deficiency through inhibiting its absorption by interfering with IF-vitamin B12 complex binding to its receptor [52].

Numerous studies have reported metformin-induced vitamin B12 deficiency. In a randomized controlled trial, a 19% decrease in vitamin B12 level with metformin treatment was found during 52 months of follow-up [53]. Another study reported that vitamin B12 deficiency (≤203 pg/mL) occurred more frequently in participants taking metformin than the placebo group [52]. The dose and duration of metformin use were also found to be associated with vitamin B12 deficiency [54,55].

Accordingly, the 2022 American Diabetes Association guidelines recommend regular measurement of vitamin B12 levels in patients taking metformin, especially those with anemia or peripheral neuropathy [56]. The efficacy of vitamin B12 supplementation has also been studied. A recent randomized controlled trial of patients with diabetic neuropathy taking metformin for at least 4 years reported that treatment with oral vitamin B12 (1 mg/d) for 1 year not only significantly increased vitamin B12 levels, but also improved neurophysiological parameters [57].

3. Colchicine

Colchicine is a medication used to prevent or treat gout flares in patients with contraindications to or intolerance of glucocorticoids and nonsteroidal anti-inflammatory drugs. Colchicine has been studied as a possible cause of vitamin B12 deficiency due to its ability to inhibit vitamin B12 absorption by reducing IF receptor levels in the ileum [58]. However, only a few studies have reported significant colchicine-induced vitamin B12 deficiency in humans [58,59].

VITAMIN D DEPLETION

1. Corticosteroids

Corticosteroids are used to reduce inflammation in various disease states. Corticosteroids may reduce calcium absorption and impair vitamin D metabolism. Dexamethasone is known to increase renal expression of vitamin D-24-hydroxylase, the enzyme that degrades the metabolites of vitamin D [60]. Vitamin D deficiency induced by corticosteroids can lead to an imbalance in bone homeostasis, resulting in bone loss or osteoporosis [61]. A representative study of the US population reported that those who used steroids within the previous 30 days had a two-fold higher risk of developing vitamin D deficiency than steroid non-users [62].

2. Antiepileptic drugs

There is growing evidence that AEDs have a negative impact on vitamin D status and bone health. Increased hepatic metabolism due to AEDs contributes to lower vitamin D levels [63]. Among AEDs, phenytoin, phenobarbital and carbamazepine are known to induce CYP3A4, the enzyme involved in the catabolism of vitamin D into its inactive form [64]. One cross-sectional study found lower vitamin D levels and bone marrow density in chronic users of AEDs compared with matched controls. The use of phenytoin was related to a greater incidence of fractures [65]. The prevalence of vitamin D deficiency in pediatric patients on AEDs was 32% [66].

3. Others

As described in the vitamin A section, orlistat and bile acid sequestrants can induce vitamin D deficiency, with vitamin D being one of the fat-soluble vitamins [67].

Table 1. Drug-induced vitamin deficiencies

Vitamin depletion	Causative medications
Lipid-soluble	
Vitamin A	Orlistat, cholestyramine
Vitamin D	Corticosteroids, antiepileptic drugs, orlistat, cholestyramine
Vitamin K	Antibiotics, orlistat, cholestyramine
Water-soluble	
Vitamin B1	Furosemide, fluorouracil
Vitamin B3	Isoniazid, pyrazinamide
Vitamin B6	Isoniazid, cycloserine, antiepileptic drugs, levodopa, theophylline
Vitamin B7	Antiepileptic drugs, lipoic acid
Vitamin B9	Methotrexate, sulfonamides, antiepileptic drugs
Vitamin B12	Acid-suppressive agents (proton pump inhibitors, H_2-receptor antagonists), metformin, colchicine

Table 2. Literature evaluations of drug-induced vitamin deficiencies

Vitamin depleted	Causative medications	Study design	Patients (or participants)	Interventions	Relevant study outcomes	Results	References
Lipid-soluble							
Vitamin A	Orlistat	Meta-analysis	10,631 participants from 16 trials (average BMI: 36.3 kg/m^2)	Orlistat 120 mg three times daily	Levels of fat-soluble vitamins (A, D, E) and beta-carotene	Orlistat therapy was associated with lower fat-soluble vitamin and beta-carotene levels	[2]
		RCT	Patients aged 30~60 years with BMI ≥30 kg/m^2	Orlistat 120 mg three times daily for 4 years	Changes in plasma levels of fat-soluble vitamins	Significant decreases in vitamin A in the orlistat group compared with the placebo group (−0.22 vs. −0.19 μmol/L, P<0.05)	[3]
	Cholestyramine	RCT	303 patients with hypercholesterolemia	Dietary advice plus cholestyramine (8 to 16 g/d for 2 months)	Serum concentrations of vitamin E, β-carotene, lycopene, and vitamin A	40% decrease in mean serum β-carotene (P<0.001) and 5% increase in vitamin A (P<0.001) after 2 months on cholestyramine	[7]
Vitamin D	Corticosteroids	Cross-sectional	NHANES participants 2001~2006 (n=22,650)	–	Prevalence of low 25(OH)D level (<10 ng/mL)	11% in steroid users vs. 5% in non-users (P=0.009)	[62]
	AEDs	Cross-sectional	58 patients on antiepileptic therapy	–	Serum 25(OH)D level Frequency of 25(OH)D <20 ng/dL	Lower levels of 25(OH)D in AED users vs. control patients (28.2±10.3 ng/mL vs. 34.4±12.7 ng/mL; P=0.02) 20 (34.4%) of AED users vs. 2 (6.8%) of controls had 25(OH)D levels <20 ng/dL (P=0.01)	[65]
	Orlistat	RCT	30 obese subjects with a mean BMI of 47 kg/m^2	Orlistat 120 mg three times daily for 1 year	Serum levels of calcitriol	140±39 pmol/L at baseline vs. 111±45 pmol/L after 1 year of orlistat therapy (P<0.05)	[68]
	Cholestyramine	RCT	268 men aged 42~68 years	Cholestyramine vs. placebo for 7~10 years	Plasma levels of calcitriol	99±190 pmol/L in placebo vs. 91±56 pmol/L in the cholestyramine group (NS)	[67]

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Table 2. Continued

Vitamin depleted	Causative medications	Study design	Patients (or participants)	Interventions	Relevant study outcomes	Results	References
Vitamin K	Antibiotics	RCT	Critically ill children who received antibiotic therapy for a minimum of 14 days	Single dose of prophylactic vitamin K on day 1 of antibiotic therapy	Incidence of vitamin K deficiency	15% of the total study population 13.3% vs. 16.7% in those with or without prophylactic vitamin K treatment, respectively (P=0.79)	[72]
		Nested case-control	Patients aged ≥20 years with or without a hemorrhagic event after using cephalosporins	–	Risk of a hemorrhagic event	aOR 1.71 (95% CI, 1.42~2.06) with the use of cephalosporins	[73]
	Orlistat	RCT	Patients aged 30~60 years with BMI ≥30 kg/m^2	Orlistat 120 mg three times daily for 4 years	Changes in plasma levels of the fat-soluble vitamins	Significant decreases in vitamin K1 in the orlistat group compared with the placebo group (–0.08 vs. 0.07 μg/L, P<0.001)	[3]
Water-soluble							
Vitamin B1	Furosemide	Prospective cohort	50 patients >18 years of age with an ICU stay of at least 48 hours	Diuretic group (furosemide 20~160 mg/d) vs. control group	Mean serum thiamin levels in the baseline and post–ICU admission days 2, 5, and 10	The diuretic group had significantly lower serum thiamin levels than the control (15.5±10.7 vs. 46.8±29.5 ng/mL; P<0.001 at baseline, 23.2±15.4 ng/mL vs. 49.0±38.0 ng/mL; P< 0.05 on day 2)	[10]
	Fluorouracil	Retrospective chart review	18 patients developed Wernicke-Korsakoff Syndrome during cancer treatment (5 of whom were taking fluorouracil)	–	Serum thiamin concentration	All patients who measured serum thiamine level (n=16) had abnormally low levels of serum thiamine (<7 nmol/L)	[17]
Vitamin B3	Isoniazid, pyrazinamide	Case report	69-year-old female with cardiac, lung, and cutaneous sarcoidosis	–	–	Decreased serum nicotinic acid levels (4.5 μg/dL) after isoniazid therapy	[21]

ACNM ANNALS OF CLINICAL NUTRITION AND METABOLISM

Table 2. Continued

Vitamin depleted	Causative medications	Study design	Patients (or participants)	Interventions	Relevant study outcomes	Results	References
Vitamin B6	Isoniazid	Single-arm clinical trial	20 patients with pulmonary tuberculosis	One week of therapy including isoniazid	Plasma levels of PLP	Decreased PLP levels in 18 patients (15 nmol/L at baseline vs. 11 nmol/L at 1 year, P<0.001)	[24]
	AEDs	Cross-sectional	Patients with epilepsy	Converted from an inducing AED (phenytoin, carbamazepine) to a non- inducing AED (levetiracetam, lamotrigine, or topiramate)	Prevalence of low vitamin B6 (<5 ng/mL)	16/33 (48%) with epilepsy vs. 1/11 (9%) of normal subjects (P<0.05) had low vitamin B6 levels Only 21% of patients had a low vitamin B6 level after switching to a non-inducing AED (P<0.05)	[28]
	Levodopa	Case report	A 75-year-old man with advanced Parkinson's disease	Levodopa/carbidopa 200/20 mg/d for 45 months		Serum vitamin B6 levels were undetectably low (<2.0 ng/mL) but normalized after vitamin B6 supplementation	[29]
	Theophylline	Single-arm clinical trial	7 healthy males	15 weeks of theophylline treatment	Mean plasma and erythrocyte PLP levels	Erythrocyte PLP levels declined from 303.3±73.2 pmoL/g to 185.1±69.2 pmoL/g within 52 days of treatment (P=0.015) Plasma PLP levels declined from 62.6±26.8 nmol/L to 29.7±14.1 nmol/L within 32 days of treatment (P=0.015)	[30]
Vitamin B7	AEDs	Cross-sectional	12 adults with seizures requiring AEDs for more than 1 year	AEDs (carbamazepine, phenytoin, phenobarbital, valproic acid, and felbamate)	Urinary excretion of biotin metabolites	There was 2.5-fold greater urinary excretion of biotin metabolites in the anticonvulsant-treated group than the control group	[33]

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Table 2. Continued

Vitamin depleted	Causative medications	Study design	Patients (or participants)	Interventions	Relevant study outcomes	Results	References
Vitamin B9	Methotrexate	RCT	113 patients with rheumatoid arthritis	Methotrexate of 7.5~25 mg/wk with or without folate supplement	Plasma homocysteine and folate levels	A decrease in serum folate level by 4.1 nmol/L (95% CI, −7.6 to −0.6) and a 3.6 μmol/L (95% CI, 1.7 to 5.6) increase in homocysteine	[40]
	Sulfonamides	Cross-sectional	23 outpatients with ulcerative colitis treated with sulfasalazine vs. 20 healthy controls	–	Blood concentrations of folate	UC patients had significantly lower folate concentrations than controls (9.8±7.3 pmol/mL vs. 23.5±9.6 pmol/mL, P=0.015)	[44]
	AEDs	Prospective	AED-treated patients (n=2,730) vs. AED-untreated patients with epilepsy (n=170) vs. healthy controls (n=200)	AEDs (carbamazepine, gabapentin, oxcarbazepine, phenytoin, primidone, or valproate)	Mean serum folate level	Mean folate level was 6.0±3.5 ng/mL in the AED-treated group vs. 6.6±3.7 ng/mL in untreated patients (P=0.044)	[45]
Vitamin B12	Acid-suppressive agents (PPIs, H_2RAs)	Meta-analysis	Four case–control studies and one observational study	Prolonged acid-suppressive agents use	Risk of vitamin B12 deficiency	HR 1.83 (95% CI, 1.36~2.46)	[48]
		Case-control	Patients aged ≥20 years	–	Risk of vitamin B12 deficiency	OR 1.65 (95% CI, 1.58~1.73) with ≥2 years use of PPIs OR 1.25 (95% CI, 1.17~1.34) with ≥2 years use of H_2RAs	[49]
		Case-control	Patients aged ≥65 years	–	Risk of vitamin B12 deficiency	OR 4.45 (95% CI, 1.47~13.34) with ≥12 months use of H_2RAs and/or PPIs	[50]
	Metformin	RCT	Patients with type 2 diabetes under insulin treatment	Metformin 850 mg or placebo three times a day for 4.3 years	Percentage change in vitamin B12 from baseline	19% decrease in vitamin B12 level compared with placebo (P<0.001)	[53]
		RCT	Impaired glucose tolerance and FBG of 95~125 mg/dL, aged ≥25 years, BMI ≥24 kg/m^2	Metformin 850 mg or placebo twice daily	Incidence of vitamin B12 deficiency (≤203 pg/mL)	4.3% of patients in the metformin group vs. 2.3% of patients in the placebo group had vitamin B12 deficiency at the 5-year follow-up (P=0.02)	[54]
		Nested case-control	Patients with diabetes receiving metformin treatment	–	Risk of vitamin B12 deficiency	aOR 2.88 (P<0.001) with 1 g/d metformin dose increment aOR 2.39 (P=0.001) for those patients using metformin for ≥3 years	[55]

BMI = body mass index; RCT = randomized clinical trial; NHANES = National Health and Nutrition Examination Survey; NS = not significant; 25(OH)D = 25-hydroxyvitamin D3; AEDs = antiepileptic drugs; ICU = intensive care unit; PLP = pyridoxal phosphate; PPIs = proton pump inhibitors; H_2RAs = H_2-receptor antagonists; FBG = fasting blood glucose; HR = hazard ratio; OR = odds ratio; aOR = adjusted odds ratio; CI = confidence interval.

ACNM ANNALS OF CLINICAL NUTRITION AND METABOLISM

Orlistat is a weight-loss agent that reduces the absorption of dietary fats by inhibiting the action of lipases within the gastrointestinal tract. Due to its mechanism of action, orlistat may disturb the absorption of lipophilic vitamins, including vitamin D. Clinical trials have shown that patients treated with orlistat compared to the placebo group showed decreased serum vitamin D concentrations after treatment [68].

Bile acid sequestrants, including colestipol and cholestyramine, are used to lower cholesterol levels. These agents could also interfere with the absorption of lipid-soluble vitamins, including vitamin D.

VITAMIN K DEPLETION

1. Antibiotics

Antibiotics are widely used to treat various bacterial infections. These drugs can contribute to a low levels of vitamin K by killing intestinal bacteria that produce vitamin K [69]. In particular, 2nd and 3rd generation cephalosporins containing N-methylthiotetrazole (NMTT) side chains are known to induce vitamin K depletion by impairing recycling of vitamin K [70].

One study reported that the incidence of vitamin K-related hypoprothrombinemia ranged from 3.7% to 64% in patients taking NMTT-containing antibiotics [71]. Another prospective study of children who received antibiotics for at least 14 days found that vitamin K deficiency occurred in 15% of the study population [72]. In addition, a nested case-control study reported an increased risk of hemorrhagic events in patients on cephalosporins, which have a known vitamin K-interfering effect. The results from these studies highlight the importance of close monitoring of vitamin K levels in patients who are at higher risk of bleeding [73].

2. Orlistat

As described in the vitamin A section, orlistat interferes with the absorption of fat-soluble vitamins, including vitamin K, by inactivating gastric and pancreatic lipases.

3. Cholestyramine

Bile acid sequestrants interfere with the absorption of bile acid in the intestine. As described in the vitamin A section, malabsorption of fat-soluble vitamins, including vitamin K, is one of the concerns when using cholestyramine. However, there are only a few reports of cholestyramine-induced vitamin K deficiency and subsequent bleeding events [74,75].

Table 1 lists specific medications related to vitamin depletion. The literature used to evaluate vitamin deficiencies is summarized in Table 2.

CONCLUSION

Drug-induced vitamin depletion has been reported in patients taking specific medications and could cause potential problems in clinical practice. Signs and symptoms related to vitamin deficiency while taking certain medications should be monitored carefully and managed appropriately if these deficiencies are clinically significant.

Although there is limited evidence regarding medication-induced vitamin depletion, an understanding of the potential risks of drug-related vitamin deficiency could help minimize adverse effects and optimize nutrition and pharmacotherapy planning, thereby improving patient outcomes.

AUTHOR CONTRIBUTIONS

Conceptualization: JWJ, SYP, HK. Investigation: JWJ, SYP, HK. Methodology: JWJ, SYP, HK. Supervision: HK. Writing – original draft: JWJ, SYP. Writing – review & editing: HK.

CONFLICTS OF INTEREST

The authors of this manuscript have no conflicts of interest to disclose.

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