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Review

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Drug-induced nutritional disorders

Nadir Yalçın, Merve Armut, Burcu Kelleci Çakır, Kutay Demirkan

Department of Clinical Pharmacy, Hacettepe University Faculty of Pharmacy, Ankara, Turkey

ORCID ID of the author: N.Y. 0000-0002-2280-8727; M.A. 0000-0002-4089-8172; B.K.Ç. 0000-0003-2547-8919; K.D. 0000-0002-6427-5826

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ABSTRACT

Nutritional disorders include malnutrition and inadequate nutrition, overweight and obesity, micronutrient disorders and refeeding syndrome. According to the European Society for Clinical Nutrition and Metabolism, sarcopenia and fragility are nutrition-related conditions with complex and multiple pathogenic infrastructure. Inadequate nutrition is also considered as protein-energy malnutrition and is often accompanied by micronutrient as well as macronutrient deficiencies. Macronutrients such as carbohydrates, proteins, and fats are essential nutrients that provide energy to the body and aid in growth. Micronutrients such as vitamins, minerals, and trace elements are necessary for many special functions in the body. Meanwhile, drug intake can lead to increased morbidity and mortality and decreased quality of life by causing malnutrition through various mechanisms. The pharmacological and pharmaceutical properties of drugs can affect the intake, digestion, absorption, storage, metabolism, and elimination of nutrients, causing imbalance in the amount of nutrients required in the body. Polypharmacy makes this situation even more risky. Many of the patients' symptoms or complaints received by physicians in their daily practice are associated with drug-induced nutritional disorders. When evaluating symptoms, physicians should also assess whether the symptoms are related to the disease, drug side effects, or drug-induced nutritional disorders. Instead of thinking that the resulting symptoms are simply "part of the disease" or "old age" and starting to take additional medication to resolve them, physicians should focus thoroughly on the event and examine what problems that the drugs used may cause in patients and the underlying reasons for deciding what they can do to eliminate them. This intervention should be investigated. Hence, this review aimed to explore the importance of the subject by mentioning the mechanisms of the negative effects of drugs on nutrition and providing examples of commonly used drugs.

Keywords: Clinical nutrition, drug, malnutrition, nutritional disorder

Introduction

Malnutrition is defined as a nutritional disorder that causes a loss of energy, protein, and other nutrients resulting from decreased food intake or digestive disorders, changes in body composition, and loss in functions, which may be accompanied by inflammation and worsen the clinical course of existing diseases (1). According to the European Society for Clinical Nutrition and Metabolism, nutritional disorders and nutrition-related conditions can be categorized as malnutrition, sarcopenia and fragility, overweight and obesity, micronutrient disorders, and refeeding syndrome (2).

Drugs affect the intake, digestion, absorption, storage, metabolism, and elimination of nutrients (3). They can disrupt food intake by causing gastrointestinal system (GIS) disorders (GIS irritation, increased acidity, endogenous digestive disorder, and gastroparesis) and digestive disorders (achlorhydria, digestive enzyme and enterocyte dysfunction, and malabsorption introduction) and affecting the intestinal system (dehydration, hypercalcemia, and hypokalemia) and the central nervous system (CNS) (CNS depression, dementia, hand tremor, and coordination disorders) (4). Moreover, the metabolism and elimination of nutrients are affected by increased energy requirements, catabolism (thyroidal and sympathomimetic drugs), organ dysfunction (hepatopathy and nephropathy), and lack of building blocks for metabolism (hypovitaminosis) (5, 6). However, anorexia can cause premature saturation, malnutrition, dysphagia, constipation, and diarrhea, affecting the sense of taste and leading to weight loss and malnutrition (5). These effects can also exacerbate subclinical malnutrition or low energy intake, especially in the elderly (7).

In this review, the effects of drugs that can cause weight loss and anorexia, nausea and vomiting, decreased GIS motility, diarrhea, dry mouth, taste and smell disorders, and obesity on nutrition disorders will be examined.

Corresponding Author: Nadir Yalçın; nadir.yalcin@hotmail.com

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Drugs that May Cause Weight Loss and Anorexia

Weight loss and anorexia are common side effects of many commonly prescribed drugs. For example, weight loss in patients with Parkinson's disease has been associated with levodopa treatment. However, this weight loss can also be attributed to the severity of the disease and the effect of movement disorders on the inability to prepare and consume food. The therapeutic use of amantadine in the treatment of patients with weight gain associated with antipsychotic drugs also causes weight loss (8).

Other drugs associated with weight loss are felbamate, topiramate, and zonisamide (9). Topiramate, which causes an increase in energy metabolism, helps prevent or treat weight gain caused by psychotropic drugs. In the United States, topiramate-phentermine combination therapy has been approved as an anti-obesity drug (8, 9). Imipramine and methylphenidate are associated with decreased appetite and are the most commonly prescribed psychotropic drugs by pediatric mental health physicians.

Another drug associated with anorexia and weight loss is sibutramine, which has been approved for weight control in adolescents and adults (3). However, considering its cardiovascular side effects (increased blood pressure and heart rate), the European Medicine Agency has suspended the licenses of sibutramine-containing drugs (10).

Furthermore, cardiac glycosides, biguanides, thiazide diuretics, angiotensin receptor blockers (ARBs), angiotensin-converting enzyme (ACE) inhibitors, potassium-sparing diuretics, acetylcholine esterase inhibitors, metformin, and penicillamine are associated with weight loss and anorexia (7, 8, 11). Sodium-glucose cotransporter-2 (SGLT-2) inhibitors and glucose-like peptide-1 (GLP-1) receptor analogues also cause weight loss (11). Meanwhile, GLP-1 agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors, which are alternative drugs to insulin and insulin secretagogues, have positive effects on weight when achieving glycemic targets (12).

Bupropion is used as the sole antidepressant for continuous weight loss in the treatment of depression and smoking cessation because of its effect on appetite reduction. Together with naltrexone, bupropion has been approved as an anti-obesity drug in the US and Europe (9). Selective serotonin reuptake inhibitors (SSRIs) (citalopram, fluoxetine, and sertraline) and selective noradrenaline reuptake inhibitors (SNRIs) (venlafaxine and duloxetine) have been associated with mild weight loss. However, this effect is temporary, and the weight increases in long-term treatment (9).

Drugs that May Cause Nausea and Vomiting

Nausea and vomiting are two of the most common side effects of drug therapy. Although they are generally observed in the early period of treatment, these symptoms may improve despite the continued treatment. Nausea and vomiting have important effects on food intake. Drug treatment may cause vomiting by a direct effect on the chemoreceptors or chemoreceptor trigger zone in the gastrointestinal tract or by joining of both pathways at the vomiting center in the medulla (8).

Cytotoxics, potassium, iron preparations, and antibiotics affect the chemoreceptors in the gastrointestinal tract, causing nausea and vomiting. However, cytotoxics, anesthetics, opiates, SSRIs, nicotine, and levodopa affect the chemoreceptor trigger zone, also causing nausea and vomiting (8). Cardiac glycosides can also cause nausea. Sulfonylureas may cause epigastric pain, heartburn, and nausea. Beta blockers may cause a decrease in gastric motility. Biguanides cause vomiting in patients with inadequate renal function (11). Nausea is also the most common side effect of acetylcholinesterase inhibitors used for treating Alzheimer's disease (13). Gastritis, peptic ulcer, and nausea associated with anorexia can also be manifested in patients with long-term high doses of aspirin (7). Drug-induced nausea, as in the case of digoxin or theophylline, may be indicate drug toxicity, which is a condition to be considered (8).

Drugs that May Reduce Gastrointestinal Motility

Decrease in gastrointestinal motility is associated with gas, bloating, and constipation, affecting oral nutrition. Drugs that stimulate anticholinergic and opiate receptors in the intestines cause slow passage and bloating. In many drugs, these symptoms are dose-dependent effects and can be minimized by reducing the dose or switching to another drug. Abdominal distension, pain, constipation, nausea, and vomiting are well-known side effects of opiate (morphine and codeine) treatment, affecting more than 50% of patients (8). In addition, tricyclic antidepressants (TCAs) and oxybutynin can reduce gastrointestinal motility, whereas beta blockers can cause constipation (11).

Drugs that May Cause Diarrhea

Diarrhea, which is one of the most common side effects of medications, occurs in cases with increased gastrointestinal motility, altered intestinal flora, and deteriorated mucosal surface. More than 25% of antimicrobial drugs are responsible for drug-induced diarrhea, which ranges from mild diarrhea to severe pseudomembranous colitis. Pen-

icillin and cephalosporins constitute the majority of cases of pseudomembranous colitis. Erythromycin increases gastrointestinal motility by acting directly on motilin receptors. Especially, lopinavir-ritonavir-combined antiretroviral therapy is also associated with diarrhea (8). Further, drugs such as irinotecan and 5-fluorouracil, which are used especially in the treatment of gastric and colorectal cancers, cause more diarrhea than other chemotherapeutics, and loperamide is routinely used to treat such diarrhea (8, 14).

Attention should also be paid to the excipients used in drugs in the form of suspension. For example, intake of sorbitol with these drugs can cause diarrhea, and intake of maltitol can cause bloating (15). Diarrhea typically ends by discontinuing these drugs. Taking the drug with food or increasing the dose may gradually reduce symptoms. This method is especially effective in diarrhea associated with metformin and iron preparations (8).

Alpha-glucosidase inhibitors used for treating diabetes can cause diarrhea and gas (11). Nauseas and vomiting are also the common side effects of acetylcholinesterase inhibitors used in the treatment of Alzheimer's disease (13). Proton pump inhibitors (PPIs) may also cause diarrhea when used for a long time (>6 weeks) (7). Biguanides, which are one of the oral antidiabetic drugs, also cause diarrhea (11).

Metoclopramide and domperidone, broad-spectrum antibiotics, misoprostol, antivirals (adefovir, tenofovir, and lamivudine), magnesium salts, acarbose, and sevelamer also cause diarrhea. Of note, the occurrence of diarrhea in patients treated with narrow therapeutic intermittent lithium, digoxin, and colchicine indicates toxicity (8).

Drugs that May Cause Dry Mouth

Saliva has many functions, such as increasing the sense of taste, facilitating speech, and protecting the mucosa. The parasympathetic pathway increases the volume of saliva produced, whereas the sympathetic pathway decreases such volume and increases the viscosity. Many drugs cause an effect on receptors affecting the saliva production, thereby causing a dry mouth and ultimately affecting the perception of flavor (8). The most common causes of dry mouth are the parasympathetic blockade by drugs with anticholinergic or antimuscarinic activity and the sympathetic stimulation caused by alpha-agonists (8).

Drugs that May Cause Taste Disorders

Disorders in taste due to drug treatment may affect patients' drug compliance and impair their food intake. Taste disorders can be classified into the following four main types: ageusia, hypogeusia, dysgeusia, and parageusia. Ageusia and parageusia are rare, whereas hypogeusia and dysgeusia are commonly associated with drug treatment (8).

Drugs that May Cause Olfactory Impairment

Odor is associated with appetite and saturation and is the first part of the cephalic phase. Food odor triggers an increase in saliva, gastrin, and insulin secretion. Decrease or change in the sense of smell affects food intake. Studies involving patients with cancer have shown that chemotherapy causes a temporary decrease in taste and smell, especially in older patients (8).

Drugs that May Cause Obesity

Obesity is one of the most important public health problems worldwide. According to WHO, approximately more than 600 million adults were obese in 2014, and 39% of them were overweight (9). Drug-induced weight gain may cause morbidity and mortality due to glucose intolerance, lipid profile deterioration, and increased blood pressure. Drugs that can cause overweight and obesity are categorized as follows:

Antidepressant drugs

Excessive weight gain during antidepressant treatment varies significantly between different classes, and it is associated with treatment duration. The use of TCA is associated with weight gain and obesity in the acute and maintenance phases of treatment. However, weight gain is not associated with the efficacy of antidepressant therapy, and it is observed when TCA is used for other indications, such as neuropathic pain or anxiety disorders. The highest weight gain is associated with amitriptyline, nortriptyline, and mirtazapine (9). Furthermore, TCAs affect the neurotransmitter pathways in the brain and exhibit antihistaminic activity that increases appetite and causes weight gain (16).

SSRIs are expected to have a weight-loss effect because of their effects on serotonin, which aids in the control of carbohydrate and food intake. In fact, in acute treatment, some SSRIs (citalopram, fluoxetine, and sertraline) and SNRIs (venlafaxine and duloxetine) are associated with mild weight loss. However, this effect is temporary, and weight gain is expected in long-term maintenance treatment (9). Although citalopram, which is an SSRI, does not show a significant weight gain, SNRIs, especially duloxetine, cause less weight gain (17). The SSRI paroxetine causes the most weight gain in long-term use, probably because of its affinity for the cholinergic receptor (9). Non-

reversible monoamine oxidase (MAO) inhibitors, such as phenelzine and tranylcypromine, also increase weight (18). Traditional antidepressants, including TCAs and MAO inhibitors, cause more weight gain than SSRIs and other recent antidepressants (17).

Antipsychotic drugs

While antipsychotic drug-induced weight gain and other metabolic effects are common side effects that increase the risk of comorbidity and mortality, the pathophysiology of antipsychotic-induced weight gain remains poorly understood. However, many studies have found a positive correlation between weight gain and therapeutic efficacy of antipsychotic drugs (19). The number of individuals taking antipsychotic drugs is relatively high. Second-generation antipsychotic drugs are often prescribed in adults as well as in children for nonpsychotic disorders, such as bipolar affective disorder, attention deficit hyperactivity disorder, and dementia in the elderly. However, 80% of the patients using this group of drugs are exposed to weight gain of 20% or more of their ideal body weight (9). Second-generation antipsychotics are the cornerstone of schizophrenia treatment. Numerous studies have linked these drugs with weight gain, dyslipidemia, insulin resistance, and type 2 diabetes (19). Drugs with high antihistaminic effects, such as clozapine and olanzapine, are the most common antipsychotics that cause weight gain (19). Nonetheless, aripiprazole, amisulpride, and ziprasidone induce minimal weight gain. Recently approved asenapine, iloperidone, lurasidone, and paliperidone cause less metabolic side effects than other antipsychotics (9). Some typical antipsychotics, such as chlorpromazine and thioridazine, may also cause weight gain, but these drugs are less commonly used due to extrapyramidal side effects (16).

Weight gain caused by antipsychotic drugs depends on the dose and duration of the drug (9). In the study of Raben et al. (19) examining patients treated with clozapine, a significant relationship was found between antipsychotic drug-induced weight gain and therapeutic efficacy after 10 weeks of treatment. Conversely, in the study conducted by Hermes et al. on patients treated with risperidone, quetiapine, and ziprasidone, no significant relationship was found on weight gain at the end of 12 weeks but appeared on the 72nd week. The relationship between antipsychotic drug-induced weight gain and therapeutic efficacy depends on the duration of treatment, but this relationship may be due to the drug treatment received by the patients in the study (19).

Lithium

In 60% of patients receiving lithium treatment for bipolar affective disorder, weight gain of more than 5% of initial body weight was detected. Risk factors for weight gain are high basal weight, younger age, gender (higher risk for women), and combined therapy with antidepressants. The mechanism of action of lithium on weight gain is unclear. Reportedly, appetite is increased due to hypothalamic effects, increased thirst and high calorie drink intake, changes in food consumption, and hypothyroidism (9).

Antidiabetic drugs

Among the antidiabetic agents, insulin, sulfonylurea, and thiazolidinediones cause significant weight gain compared with placebo. Sulfonylurea-induced weight gain is approximately 4 kg in the first year of treatment; it is apparent in the first months of treatment and then plateaus (9). In a 27-week study of 845 patients with type 2 diabetes who received gliclazide or glimepiride once a day, body weight increased by approximately 0.6 kg in both groups. Similarly, weight gain was observed in patients treated with repaglinide and nateglinide. A randomized, multicenter, 16-week clinical trial study compared the efficacy and safety of repaglinide and nateglinide monotherapy in patients with type 2 diabetes who were previously treated with diet and exercise. The study found that the average weight gain was 1.8 kg in the repaglinide group, whereas it was 0.7 kg in the nateglinide group. These studies show that insulin secretagogues are associated with weight gain in patients with diabetes. Meanwhile, glyburide is a sulfonylurea drug that causes the most weight gain (12).

Thiazolidinediones are insulin-sensitizing drugs that reduce insulin resistance in peripheral tissues and minimize hepatic blood glucose production. Weight gain was observed more in patients who responded better to thiazolidinedione treatment (12). This drug causes 1.5-4 kg weight gain in the first year of treatment, depending on the dose and duration of use (9). In a clinical trial study of pioglitazone, which included 5238 patients with type 2 diabetes, an average of 3.8 kg weight gain was observed over a three-year period with the use of pioglitazone. According to a clinical study of 4360 patients who were first treated with rosiglitazone, metformin, and glyburide for newly diagnosed type 2 diabetes, those who received rosiglitazone gained an average weight of 4.8 kg. Weight gain caused by thiazolidinedione use may result from the renal excretion of sodium and fluid retention. When rosiglitazone is used in combination with metformin, weight can be reduced or remained unchanged (12).

Some patients with type 2 diabetes may require insulin therapy for a period of time to achieve glycemic control (9). One study found a significantly higher weight gain in patients receiving insulin (4 kg) compared with those receiving chlorpropamide (2.6 kg) or glibenclamide (1.7

kg). Patients receiving insulin therapy generally gain 2-3 kg over a period of 6-12 months. This weight gain is less common in metformin-combined therapy than in insulin monotherapy, due to the insulin dose and/or the attenuating effects of metformin. The anabolic properties of insulin can lead to weight gain by increasing protein synthesis and inhibiting lipolysis and proteolysis, resulting in increased lean body mass. In some studies, insulin detemir causes less weight gain than neutral protamine Hagedorn (NPH) insulin. For example, in a 26-week multicenter randomized study of 504 patients with type 2 diabetes from 91 centers in the US and Europe, patients receiving insulin detemir (1.0 kg) gained significantly less weight than those receiving NPH insulin (1.8 kg). The weight difference between insulin detemir and NPH insulin appears more pronounced when insulin detemir is administered at night. The evidence suggests that insulin detemir and insulin glargine have a similar effect on glycemic control and that insulin detemir does not provide weight gain (12).

In conclusion, drug-induced weight gain should be monitored in patients with diabetes using oral antidiabetic agents and insulin to increase compliance with treatment and reduce metabolic side effects.

Antihypertensive drugs

Hypertension is one of the common comorbidities of obesity and type 2 diabetes. Therefore, drugs that increase weight gain or have other metabolic side effects are a significant concern in hypertensive patients with obesity (9). Thiazide diuretics are generally recommended as first-line agents for treating hypertension but are not recommended for patients who are overweight or obese and at risk of metabolic syndrome and type 2 diabetes, due to dose-related side effects such as dyslipidemia and insulin resistance (20). Patients receiving beta blockers generally tend to increase in weight. At the end of the first year of beta-blocker treatment, a 4 kg increase was detected (9). Beta blockers may either increase weight gain or prevent weight loss, especially in patients with both hypertension and diabetes. Hence, beta blockers should not be the first-line treatment for hypertension in patients with overweight or obesity, considering that weight control is more difficult in patients with hypertension treated with beta blockers (20). Given the effects of beta blockers on body weight, around 4%-9% is reduced in total energy expenditure of patients. Beta-blocking agents reduce the basal metabolic rate by 12% in hypertensive patients with obesity compared with other antihypertensive drugs. Beta blockade also prevents lipolysis in response to adrenergic stimulation, making weight loss difficult for patients. It can also cause fatigue and tiredness in patients, thereby preventing exercise (9). Selective agents such as carvedilol and nebivolol are recommended for patients who require beta blockers; such patients include those with coronary artery disease, heart failure, or arrhythmia. These drugs have less potential for weight gain and have minimal effect on lipid-glucose metabolism. In a study involving 1106 patients with hypertension, weight gain of patients receiving metoprolol significantly increased compared with that of patients receiving carvedilol. While 4.5% of the metoprolol group gained more than 7% of their weight, such weight gain percentage was only found in 1.1% of carvedilol users. Therefore, weight gain can be minimized by selecting a different drug in the same group (20).

ACE inhibitors, ARBs, and calcium channel blockers are not associated with weight gain and insulin resistance. Considering that angiotensin is overexpressed in obesity, ACE inhibitors and ARBs have positive effects on obesity-related hypertension. These drugs become targeted options for the treatment of patients with obesity. Furthermore, given that many of these patients suffer from type 2 diabetes or prediabetes, they are likely to benefit from kidney protection through ACE inhibitors and ARBs (20). In conclusion, when controlling hypertension, physicians should select the most suitable antihypertensive drug, especially in patients at risk for obesity.

Steroid hormone drugs

Glucocorticoids stimulate appetite by altering the activity of protein kinase activated by adenosine monophosphate in the hypothalamus, and they affect dietary intake by increasing dietary fat requirement (9). Secondary to long-term glucocorticoid treatment, Cushing's syndrome occurs when body fat accumulates to cause truncal obesity, buffalo hump, and a moon face. The risk of these complications varies depending on both the dose and the duration of treatment. In patients with rheumatoid arthritis, the use of prednisone at 5-10 mg/day for two years is associated with an increase in the average body weight of 4%-8% (21). Weight gain caused by glucocorticoid treatment may be more than 10 kg in approximately 20% of patients in the first treatment year (9). Corticosteroids injected locally into the knee joint or spinal column for inflammation and inhaled corticosteroids used for asthma are not associated with weight gain (16). Synthetic anabolic steroids, such as oxandrolone, are increasingly used to reduce catabolism and weight loss experienced by critically ill patients (8, 22). In conclusion, metabolic side effects should be monitored in patients receiving long-term high-dose steroid therapy to minimize weight gain.

Synthetic progestins

Only progestin-containing birth control pills are used by women who cannot take estrogen to prevent pregnancy (23).

Although weight gain is generally known as a side effect of hormonal contraception, combined contraceptives are not associated with weight gain. However, while weight generally increases among patients using depot medroxyprogesterone acetate, information about other progestins is limited (24).

In a study conducted in the USA, more women gained weight when using depot medroxyprogesterone acetate than when using low-dose oral contraceptives (23). Medroxyprogesterone acetate is an approved drug for treating anorexia, cachexia, or unexplained weight loss in patients with acquired immunodeficiency syndrome in the USA (24). However, data supporting its use in cancer cachexia are also available. This drug has significant effects on appetite, weight gain, and health-related quality of life (8). When synthetic progestins are used, especially in adolescents, some weight gain may be regarded as developmentally normal and appropriate. Therefore, the possible causal relationship between contraceptives and weight gain is difficult to examine (24).

Antiepileptic Drugs

Most weight changes associated with antiepileptic drug therapy occur in the first 3 months after onset (25). Among the antiepileptic drugs, valproate and carbamazepine exhibited the most significant weight gain. Weight gain is observed in 71% of patients using valproate and 43% of patients using carbamazepine. Pregabalin and gabapentin can also cause weight gain. Antiepileptic drugs that have no effect on weight change are lamotrigine, levetiracetam, and phenytoin. Weight gain caused by valproate intake is the highest in the first year of treatment, with a higher incidence in women than in men. In addition, weight gain is higher in patients who are overweight before the start of treatment (9).

Histamine-1 (H1) receptor blockers

H1 receptor blockers are widely used as sedative and antiallergenic, and weight gain is one of their possible side effects. According to the 2005-2006 National Health and Nutrition Examination Survey, patients using H1 receptor blockers (cetirizine, fexofenadine, and desloratadine) had significantly higher weight, waist circumference, and insulin levels. However, further research is needed to determine the role of histamine in energy metabolism (26).

Drugs that May Cause Micronutrient Disorders

Micronutrients are indispensable for vital functions but are a global problem for two billion people worldwide. The effects of drugs on nutrients may lead to a reduction or depletion of micronutrients in various ways (27). In a study on 390 geriatric patients with drug-induced micronutrient deficiency, antacids caused phosphate deficiency (32.8%); digoxin potassium, calcium, and magnesium deficiency (29.5%); and bisacodyl vitamin D, vitamin K, potassium, and calcium deficiency (29%) (28). Drugs with effects such as inducing micronutrient metabolizing enzymes, inactivating digestion-related enzymes, complex formation, oral mucosal and intestinal flora damages, impaired gastrointestinal motility, changes in pH, loss of appetite, nausea, vomiting, diarrhea, and constipation can disrupt the absorption, distribution, and metabolism of micronutrients and can increase intestinal and renal excretions (29).

Acid-suppressing drugs

H2 receptor antagonists and PPIs are commonly prescribed for treating gastroesophageal reflux disease and peptic ulcer. These drugs cause various nutritional deficiencies (30). They can block histamine and reduce acid secretion, thereby reducing the absorption of calcium, iron, zinc, folic acid, vitamins D, and vitamin B12 and ultimately resulting in micronutrient deficiencies (29, 31).

PPIs reduce gastric acid production by up to 99% by decreasing the effect of proton pumps, which are a part of the stomach acid production mechanism. This action causes micronutrient deficiencies by decreasing the absorption of vitamin B12 and magnesium (29). Sufficient gastric acid is required for vitamin B12 absorption. Both PPI and H2 blockers significantly increase the risk of vitamin B12 deficiency in elderly patients, especially because these patients do not have sufficient gastric pH for B12 absorption (30). Thiazide-induced hypercalcemia may be significant enough to mask PPI-induced hypocalcemia and hypomagnesemia. Therefore, physicians should remember that long-term concomitant use of PPI and H2 blockers may lead to electrolyte imbalance (32).

Antibiotics

Antibiotics can reduce the absorption of micronutrients, form complexes, induce enzymes, cause mucosal damage, chelate, and reduce the endogenous production of micronutrients (29). Thus, deficiency in antibiotic-induced vitamins B1, B2, B3, B5, B6, B12, A, D, and K; folic acid; iron; calcium; magnesium; and potassium may occur (29, 30, 33). While fluoroquinolones cause calcium and iron deficiencies, tetracyclines can inhibit the absorption of vitamin B6, calcium, magnesium, iron, and zinc in the gastrointestinal tract when they bind to this type of drug (30, 34). Moreover, trimethoprim causes folic acid deficiency; penicillin and cephalosporins cause B and K vitamin deficiencies; and aminoglycosides, such as gentamicin, neomycin, and streptomycin, cause magnesium, calcium and potassium imbalance, and vitamin B and K deficiencies (30, 34).

Cardiovascular drugs

Beta blockers reduce the blood pressure by decreasing the effects of catecholamines, thereby reducing the heart rate. Beta blockers interfere with the production of this essential enzyme for energy production, leading to CoQ10 deficiency. Given that the target condition is a cardiovascular disease, the lack of CoQ10 is particularly dangerous. The presence of CoQ10 deficiency, which is needed in high amounts by mitochondria in the heart, increases the risk of heart failure (30). Digoxin, which is used for treating arrhythmias, increases renal elimination and causes magnesium, potassium, calcium, phosphorus, and vitamin B1 deficiencies (29).

Some antihypertensive drugs cause micronutrient deficiencies by increasing the renal elimination of micronutrients or by decreasing the functionality of cell work (29). Loop and thiazide diuretics cause deficiency in sodium; potassium; magnesium; vitamins B1, B6, and C; zinc; and CoQ10. Meanwhile, thiazide diuretics increase calcium, whereas loop diuretics reduce calcium content in the body. While potassium-sparing diuretics increase the amount of potassium, they also cause calcium, folic acid, and zinc deficiencies (34). ACE inhibitors also increase potassium levels while causing zinc deficiency (34, 35). Routine electrolyte monitoring is recommended in high-risk patient groups (pediatric and geriatric patients with renal failure), especially when using antihypertensive drugs that cause electrolyte imbalance.

Oral antidiabetic drugs

Vitamin B12 absorption decreases in patients with diabetes using metformin (29, 36). Metformin causes vitamin B12 deficiency in a dose- and time-dependent manner. According to the American Diabetes Association, vitamin B12 levels should be routinely checked in patients taking metformin, considering that B12 deficiency is associated with significant side effects, such as anemia and cognitive impairment (7, 37). Serum folic acid levels also decrease in patients with type 2 diabetes on metformin therapy. Vitamin B12 and folic acid depletion increase the homocysteine levels. In addition, metformin can reduce the CoQ10 levels, increasing the risk of heart disease (30). According to a cross-sectional study, a significantly higher rate of malnutrition was found in patients receiving two or more antidiabetic medication (38).

Statins

Commonly prescribed statins cause CoQ10 and vitamin D deficiencies (29, 30). Statins block the activity of 3-hydroxy 3-methylglutaryl coenzyme-A (HMG-CoA), which is an enzyme necessary for cholesterol production in the body. This blockade leads to the lack of CoQ10, which requires HMG-CoA for its production. Thus, harmful effects on muscle and heart health may occur. Therefore, daily supplementation of 100-200 mg of CoQ10 is recommended for patients using statins (30).

Anti-inflammatory drugs

Nonsteroidal anti-inflammatory drugs cause iron and folic acid deficiencies, whereas salicylates cause iron, folic acid, potassium, sodium, vitamin C, and vitamin B5 deficiencies. These drugs reduce the absorption and function of micronutrients in the cell (29). Prolonged use of high doses of aspirin is associated with gastric mucosa irritation, gastritis, peptic ulcer disease, nausea, anorexia, malnutrition, and decreased vitamin C levels. However, evidence of vitamin C reduction or that vitamin C supplementation is needed in patients receiving chronic low-dose aspirin is unavailable (7). Furthermore, patients using steroids (prednisone, methylprednisolone, triamcinolone, and dexamethasone) can experience deficiency in calcium; magnesium; zinc; vitamins B6, B12, C, and D; folic acid; selenium; and chromium (34).

Psychotropic drugs

For antidepressant drugs to work best, vitamin B must be present as sufficient cofactors to help produce the necessary neurotransmitters, such as serotonin and dopamine. Therefore, these drugs may not directly reduce the level of vitamin B, but patients should be known whether they have vitamin B deficiency (30). SSRIs can cause folic acid deficiency, TCAs and phenothiazines can cause CoQ10 and B2 vitamin deficiencies, benzodiazepines can cause calcium deficiency, and haloperidol can cause CoQ10 deficiency (29). In addition, lithium carbonate used for treating bipolar affective disorder can cause folic acid and inositol deficiencies (30).

Antiepileptic drugs

Antiepileptic drugs cause micronutrient deficiencies by reducing their absorption and increasing their metabolism, enzyme induction, and chelation. Barbiturates cause calcium, folic acid, vitamin D, and vitamin K deficiencies. Phenytoin also causes deficiency in calcium, folic acid, vitamins B1, B2, and D, and carbamazepine causes folic acid and vitamin D deficiencies. Meanwhile, valproic acid is associated with L-carnitine deficiency (29). In a study conducted by Mintzer et al. on 33 patients, enzyme-inducing antiepileptic drugs (phenytoin and carbamazepine) caused more vitamin B deficiency than non-enzyme-inducing antiepileptic drugs (levetiracetam, lamotrigine, and topiramate) ($p<0.05$) (39).

Hormone replacement therapy and oral contraceptives

Hormone replacement therapy and oral contraceptives lead to deficiencies by decreasing the absorption of mi-

cronutrients and increasing their metabolism and elimination (29). These drugs may cause deficiency in folic acid; vitamins B1, B2, B3, B6, B12, and C; magnesium; selenium; and zinc (34).

Other drugs

Methotrexate causes folic acid deficiency by reducing the functionality of secondary folate required for pyrimethamine, pentamidine, triamterene, and dihydrofolate reductase inhibition. Methotrexate also causes vitamin D deficiency, resulting in oral mucositis (40). Meanwhile, sulfasalazine causes folic acid deficiency by disrupting the absorption and metabolism of intestinal folate (3).

Isoniazid forms a complex with pyridoxine, causing increased urinary excretion of pyridoxine and leading to the lack of pyridoxine. Niacin synthesis is impaired due to pyridoxine deficiency; patients using isoniazid were found to have both pyridoxine and niacin deficiencies (3).

Cholestyramine induces cytochrome P 450 enzyme, resulting in the deficiencies of vitamins D, E, and K. This drug also causes folic acid deficiency (3).

Amphotericin causes potassium deficiency by increasing the renal loss of potassium, accompanied with magnesium deficiency (3, 35). In addition, foscarnet, which is a nephrotoxic drug, causes calcium, magnesium, and potassium deficiencies (34).

Vitamin B12 deficiency, which elevates the risk of chemotherapy-induced peripheral neuropathy, is increased especially when using the taxol-containing chemotherapeutic agents, leading to neurotoxic effects (41).

Effect of Drugs on Clinical Nutrition

Parenteral nutrition (PN) is generally administered as an intravenous infusion with the simultaneous administration of medications; thus, PN may be a suitable carrier. Adding a drug into the PN bag is a common practice because it does not need additional fluid in patients with fluid restriction, requires less venous catheters, and reduces the administration time. However, adding drugs into parenteral and enteral nutrition mixtures is not recommended because of the high risk of stability and incompatibility problems (35).

Feeding can often be frequently interrupted because of the administration of medication through the feeding tube. In this case, the infusion rate must be increased appropriately to meet the required caloric requirement; otherwise, this event results in malnutrition. For high-dose catecholamine users with hemodynamic instability, enteral nutrition should be interrupted until their hemodynamics stabilizes; meanwhile, caution should be exercised in enteral nutrition for low-dose catecholamine users (35). Adequate gastrointestinal blood flow is required for proper absorption and use of nutritional products. Considering that patients are not hemodynamically stable in cases such as sepsis, hemorrhage, hypovolemia, polytrauma, and cardiogenic shock, vasoactive agents, such as norepinephrine, epinephrine, phenylephrine, dopamine, and dobutamine, are needed to reserve blood flow to vital organs, including the heart and the brain. Hence, gastrointestinal blood flow decreases. If increased oxygen demand in the intestine cannot be met due to enteral nutrition, intestinal ischemia and rarely, small intestine necrosis with high mortality risk may occur. Given that ischemia in the intestine and necrosis in the small intestine are feared complications, application of enteral nutrition should be avoided as much as possible in patients requiring vasoactive substances (35).

Management of Drug-Induced Malnutrition

Patients with malnutrition should be monitored closely when initiating a medication and regularly reviewed to ensure that any weight loss can be detected quickly and corrective measures are taken. When attempting to increase weight gain, a multimodal approach is necessary, the dietician should be consulted, and healthy dietary recommendations should be given (8).

For drugs that may cause nausea and vomiting, an appropriate antiemetic drug can be selected to determine possible receptor stimulation. In a study conducted by Davidson et al. on 121 patients with cancer who had chemotherapy, chemotherapy-induced nausea and vomiting, which require urgent intervention, were detected in 26% of patients (42). Drug-induced nausea and vomiting should be closely monitored in such patients who are highly at risk. However, of note, drug-induced nausea and vomiting may indicate drug toxicity, such as digoxin or theophylline toxicity. The choice of antiemetic should not destroy the desired therapeutic effect of the targeted treatment. For example, the use of metoclopramide in nausea associated with levodopa treatment worsens Parkinson's symptoms due to central dopamine blockade (8).

For many drugs, reduced gastrointestinal motility is a dose-dependent effect, which can be minimized by lowering the dose or changing the preparation. The diet plan includes adequate oral or enteral fluid therapy and fiber supplementation. A multidisciplinary approach is needed to manage constipation, which may adversely affect

the quality of life of patients (8). Diarrhea spontaneously passes for most drugs or ends with drug discontinuation. Taking drugs with food and re-adjusting the dose of drugs may gradually reduce the symptoms (8).

In dry mouth, the severity of symptoms can be reduced by using a modified release preparation of the drug or by dividing the dose. If an alternative drug in the same class can achieve the desired therapeutic effect with fewer symptoms, then drug change is necessary. If discontinuing the drug that reduces patient compliance is not an option, the timing of drug administration should be adjusted to minimize the effect on oral intake and mealtime. In severe cases, the use of saliva stimulants and artificial saliva products may be appropriate (8).

Drug-induced taste disorders may be managed by researching for other reasons, such as dry mouth or depression, and when identified, taking corrective measures. Discontinuation of this drug should be considered when a clear association with a particular drug is identified. If discontinuing the responsible drug is not possible, using lozenges containing oral spray and local anesthetics may be beneficial (8).

Weight gain in the first month after treatment is a strong indicator of long-term weight gain. Therefore, patients should be monitored before and shortly after starting weight-gaining medications, and an increase of 5% above the baseline weight after the first month should encourage physicians to reconsider treatment options or initiate weight control strategies (9). Given that insulin, sulfonylurea, and thiazolidinediones are antidiabetic agents that cause significant weight gain, metformin and DPP-4 inhibitors can be used as alternatives because they do not cause weight gain. Furthermore, SGLT-2 inhibitors and GLP-1 receptor analogues cause weight loss. The effects of insulin on body weight can be reduced by adding metformin. With the new pharmacological classes, the effects of drugs on weight can be reduced, and even weight loss can be achieved (9).

Appropriate dietary strategies specific to the patient should be developed in drug-induced micronutrient disorders. In addition, considering that antibiotics affect the beneficial bacterial flora, including *Lactobacillus acidophilus* and *Bifidobacterium bifidum* in the digestive tract, probiotic intake is recommended in patients using antibiotics (30).

Conclusion

For preventing drug-induced nutritional disorders and the undesirable effects of these disorders, physicians and other healthcare providers need to accomplish the following: diagnose the disease properly, re-evaluate the selected treatment frequently, identify the treatments and disease stages necessary to minimize the number of drugs given, make a rational nutritional assessment, and if necessary, plan the optimal nutrition therapy to avoid adverse effects of drug-induced nutritional disorders.

The entire multidisciplinary team should be aware of the possible effects of drug treatment on nutritional status. Any nutritional assessment should include observation and intervention regarding the patient's medication. At this point, clinicians' should identify and analyze drug-induced nutritional disorders and minimize risk factors at the most appropriate time with the most appropriate way.

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