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Educational Paper

LLL 44 - 2 — Micronutrients in clinical nutrition: Vitamins

Karin Amrein [a], Angélique M.E. de Man [b], Oguzhan S. Dizdar [c], Kursat Gundogan [d], Michael P. Casaer [e], Hanna-Liis Lepp [f], Serge Rezzi [g], Arthur RH. van Zanten [h], Alan Shenkin [i], Mette M. Berger [j,*], for the ESPEN Micronutrient Special Interest Group (SIG-MN)

[a] Medical University of Graz, Department of Internal Medicine, Division of Endocrinology and Diabetology, Austria
[b] Amsterdam UMC, Location Vrije Universiteit, Department of Intensive Care, Amsterdam Cardiovascular Sciences, Amsterdam, the Netherlands
[c] Department of Internal Medicine and Clinical Nutrition Unit, University of Health Sciences Kayseri City Training and Research Hospital, Kayseri, Turkey
[d] Division of Intensive Care Medicine, Department of Internal Medicine, Erciyes University School of Medicine, Kayseri, Turkey
[e] KU Leuven, Department of Cellular and Molecular Medicine, Laboratory of Intensive Care Medicine, Leuven, Belgium
[f] North Estonia Regional Hospital, Tallinn, Estonia
[g] Swiss Nutrition and Health Foundation, Epalinges, Switzerland
[h] Gelderse Vallei Hospital, Ede and Division of Human Nutrition and Health, Wageningen University & Research, Wageningen, the Netherlands
[i] Institute of Aging and Chronic Disease, University of Liverpool, Liverpool, UK
[j] Faculty of Biology & Medicine, Lausanne University, Lausanne, Switzerland

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SUMMARY

Vitamins are essential organic molecules, which are required in the diet in relatively small amounts in any form of nutrition (oral, enteral, parenteral). Despite the small amounts that are required, the vitamins are essential both for maintenance of health, growth, and treatment of disease.

After reminding about the principal function of all the vitamins, their needs and the clinical consequences of their deficit, the text present some common clinical problems: the impact of inflammation on the assessment of status. The reasons and diseases which cause increased requirements are presented, with the indications to monitoring of blood levels which remain the classical way to assess status in clinical settings.

The text summarises the most relevant clinical manifestations of vitamins depletion and deficiency, the difficulties in assessing status, and makes recommendations for provision for medical nutrition therapy.

* Corresponding author.
E-mail addresses: karin.amrein@medunigraz.at (K. Amrein), ame.deman@amsterdamumc.nl (A.M.E. de Man), oguzhansitki.dizdar@sbu.edu.tr (O.S. Dizdar), kursatgundogan@gmail.com (K. Gundogan), michael.casaer@uzleuven.be (M.P. Casaer), liis.lepp@gmail.com (H.-L. Lepp), serge.rezzi@nutritionhealthfoundation.ch (S. Rezzi), arhvanzanten@gmail.com (A.RH. van Zanten), shenkin@liverpool.ac.uk (A. Shenkin), mette.berger@unil.ch (M.M. Berger).

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Abbreviations:

DRI	daily recommended intake
CRP	C-reactive protein
DFE	dietary folate equivalent
FMN	flavin mononucleotide
FAD	flavin adenine dinucleotide
FSMPs	Food for Special Medical Purposes
MNT	medical nutrition therapy
MN	micronutrient
NAD, NADP, NADH, NADPH	Nicotinamide-Adenine Dinucleotides
PLP	pyridoxal phosphate
PN	parenteral nutrition
RBC	red blood cell
RBP	retinol binding protein
RDA	Recommended Dietary Allowances
ROS	reactive oxygen species
ThDP	Thiamine diphosphate
TPP	thiamine pyrophosphate
TPN	Total parenteral nutrition
25(OH)D	vitamin D3

Learning objectives

- To list the vitamins which need to be supplied to patients receiving medical nutrition therapy (MNT)
- To know the clinical impact of vitamin deficiency
- To understand the reasons why patients receiving MNT may have increased requirements.
- To understand the value and limitations of methods of assessing vitamin status in patients receiving MNT

Key messages

- Vitamins are an essential part of any form of nutrition, both in normal individuals and in those requiring nutrition therapy
- Patients requiring intravenous nutrition (PN) should receive vitamins together with trace elements from the beginning of the PN.
- Requirements in disease are often greater than in health to cope with increased metabolic requirements and increased losses.
- The inflammatory response complicates the assessment of their status and requires the simultaneous assessment of the level of inflammation using C-reactive protein (CRP) as a biomarker.
- Monitoring of vitamins may require the determination of additional functional biomarkers.

1. Vitamins – functions

The functions, biochemical model of action, effects of deficiency, and recommended methods of assessment of the different vitamins are summarized in Table 1.

1.1. Vitamin B1 (thiamine)

Thiamine is an essential water-soluble vitamin for carbohydrate and energy metabolism [1]. It acts as a cofactor for enzymes involved in mitochondrial energy production as ATP and synthesis of essential cellular molecules: neurotransmitters acetylcholine and γ-amino butyric acid (GABA) and nucleotides, and control of oxidative stress. Absorption of thiamine occurs in the jejunum and ileum [2] and can be inhibited by alcohol consumption, or by folate deficiency [3]. In adults the Recommended Dietary Allowances (RDAs) is 1.1–1.2 mg/day [2]. In humans, body stores of thiamine are limited and dependent on dietary thiamine intake.

Thiamine diphosphate (ThDP) is the active form also called thiamine pyrophosphate (TPP). Thiamine status should be determined by measuring red blood cell (RBC) or whole blood ThDP as a direct method. If RBC or whole blood ThDP determination is not available, measurement of red cell transketolase and its activation by thiamine may be considered as an indirect method [4]. To confirm diagnosis of deficiency, a thiamine supplementation trial should be performed to assess clinical benefit since treatment should not be delayed by waiting for the laboratory result.

Patients at risk for thiamine deficiency are numerous, and include those with malnutrition, poor oral intake and chronic alcohol consumption, malignancies, and increased metabolic requirements (pregnancy, lactation) [5]. Often, multiple factors coexist. Insufficient dietary intake, especially in combination with increased metabolic needs due to oxidative stress and systemic inflammation in critical illness (trauma, sepsis, cardiac arrest, and after cardiac surgery), can quickly generate a state of thiamine deficiency. Reduced gastrointestinal absorption due to disease or surgery (resections), increased gastrointestinal or renal losses (chronic diuretic therapy or continuous renal replacement therapy) should also be considered.

The Dietary Refrence Intake (DRI) and /RDA for thiamine are 1.1–1.2 mg/day, but the recommended doses for parenteral nutrition (PN) are 2–5 mg and 1.2–10 mg for enteral nutrition (EN), increasing to 100 mg in the actuely ill patients. Clinical thiamine deficiency may present as a range of clinical signs and symptoms involving the neurological, psychiatric, and cardiovascular systems [4]. The neurological symptoms range from mental changes such as apathy, decrease in short-term memory, confusion, and irritability to cognitive deficits and the Wernicke-Korsakoff encephalopathy, optic neuropathy, and central pontine myelinolysis [6]. The involvement of other organs manifests as in beriberi, congestive heart failure, or unexplained metabolic lactic acidosis [5]. Among the thiamine disorders, the refeeding syndrome is of particular concern in inpatients and is associated with increased mortality (please see LLL 44-4) [7,8].

1.2. Vitamin B2 (riboflavin)

Riboflavin is involved in redox reactions and antioxidant functions, and metabolism of other B vitamins (niacin, B6, B12, and folate) in the form of flavoproteins. Intracellular metabolism involves phosphorylation of riboflavin to form the cofactors flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD),

Table 1
Vitamins - Functions, biochemical model of action, effects of deficiency and methods of assessment.

	Metabolic Functions	Biochemical modes of action	Effects of deficiency	Assessment of Status	Comments
Vitamin A	Visual acuity. Antioxidant Growth and development. Immune function.	Rhodopsin in retina. Free radical scavenger Induces DNA transcription	Xerophthalmia. Night blindness. Increased risk of infections.	Plasma retinol. Plasma retinol binding protein.	Fall in retinol during acute phase response due to fall in retinol binding protein.
B1 (thiamine)	Carbohydrate and energy metabolism.	Decarboxylation reactions as ThDP	Beri–Beri with neurological, & cardiac effects. Wernicke Korsakoff Syndrome	RBC or whole blood ThDP or RBC transketolase	Deficiency may occur and is reversed rapidly.
B2 (riboflavin)	Oxidative metabolism and immunomodulation.	Coenzyme as FAD or FMN	Lesions of oral, buccal and skin. Possibly immune function↓	RBC glutathione reductase	Constant dietary supply is needed.
B6 (pyridoxine)	Carbohydrate, protein, and lipid metabolism.	Coenzyme as PLP	Microcytic anaemia Lesions of lips and skin Epileptiform convulsions, confusion, and depression	Plasma PLP levels	
B3 Niacin	Conversion of nutrients into energy. DNA forming and repairing. Antioxidant.	Coenzyme as NAD/NADP.	Pellagra-rash, weakness, diarrhoea and dementia	Blood or tissue NAD levels	**Potential protective role in** acute kidney injury **is under investigation**
Folate	Amino acid, Purine/ pyrimidine metabolism	Single carbon transfer	Megaloblastic anaemia	Serum folate RBC folate	Recent intake Whole body status
Biotin	Lipogenesis/ gluconeogenesis Immune function	Carboxylase reactions.	Scaly dermatitis. Hair loss. Neurological complications	Blood and urine biotin	Rarely assayed.
Vitamin C	Collagen synthesis Antioxidant Facilitates absorption of iron	OH proline/OH lysine synthesis Reduction reactions including $Fe^{+++} \rightarrow Fe^{++}$	Scurvy, impaired wound healing Impaired immune function Oxidative damage	Leukocyte vitamin C Plasma vitamin C	Plasma vitamin decreases in inflammation
Vitamin D	Calcium absorption Differentiation of macrophages	Receptor mediated transcription	Osteomalacia (adults) Rickets (children) Immune status ↓	Serum Ca/P/alkaline phosphatase Serum 25(OH)D, 1,25 $(OH)_2$ vit D	
Vitamin E	Antioxidant in membranes	Free radical scavenger	Haemolytic anaemia Atherosclerosis Certain neoplasia	Plasma tocopherol/ cholesterol	Vitamin E is transported in LDL
Vitamin K	Blood coagulation Bone calcification	A-glutamyl carboxylation Coagulation proteins and osteocalcin	Bleeding disorders Bone disorders	Prothrombin time Plasma phylloquinone	Time consuming assay

Abbreviations: NAD/NADP = Nicotinamide-Adenine Dinucleotides; RBC = red blood cell; PLP = pyridoxal phosphate; ThdP = Thiamine diphosphate.

which account for most of riboflavin in plasma and tissues. FAD and flavin mononucleotide (FMN) serve as electron carriers in various redox reactions of energy production and metabolic pathways, including carbohydrate, lipid, and amino acid metabolism, mitochondrial oxidation, and various antioxidant functions. It is needed for B6 (pyridoxol) conversion to pyridoxal (aldehyde form) and neurotransmitter metabolism. Riboflavin is also required for normal antibody production and has several immunomodulatory effects.

Riboflavin is absorbed from the proximal small intestine. It is not stored in the body in ample amounts, making a constant dietary supply a necessity [9]. The RDA of riboflavin in males is 1.3 mg, in females 1.1 mg. In plasma, riboflavin, FMN, and FAD are all associated with plasma proteins such as albumin.

The RDA of riboflavin in males is 1.3 mg, in females 1.1 mg, and 1.4 mg and 1.6 mg during pregnancy and lactation, respectively. The dose recommended in PN is 3.6-5 mg [7]. Assessment of riboflavin status can be required when there is clinical suspicion of deficiency. Deficiency is manifested with oral-buccal lesions (cheilosis, glossitis, and angular stomatitis), seborrheic dermatitis of the face, trunk, and scrotum. Other manifestations are ocular (itching, burning, dryness, corneal inflammation, and photophobia), and normochromic, normocytic anemia and marrow aplasia (9). Since plasma riboflavin was consistently decreased in the context of inflammation, the riboflavin status should be assessed by the glutathione reductase activity in RBCs [10].

1.3. Vitamin B3 (niacin)

Niacin is a collective term for nicotinic acid and nicotinamide. All tissues in the body convert absorbed niacin into its main metabolically active form, the coenzyme NAD and NADP. NAD is the main coenzyme responsible for nutrient oxidation and energy production, serving as the main entry for the respiratory chain and contributing to mitochondrial oxidation processes. NADPH is the main player in reductive biosynthesis, like the production of fatty acids, cholesterol, and steroid hormones. NADPH exerts strong antioxidant effects, particularly in blood cells (in RBC, regeneration of Hb), in PMN generated oxidation burst. NADPH oxidases (NOXs) form a family of electron-transporting membrane enzymes whose main function is reactive oxygen species (ROS) generation [11]. NADPH is needed to reduce folate (B9) to its active form of tetrahydro folic acid.

The DRI of niacin is 16 mg/day and 14 mg/day for adult males and females, respectively [12]. Niacin deficiency usually occurs in less developed countries and is associated with low animal protein and amino acid tryptophan intake, which serves as a precursor of intrinsic niacin synthesis. Clinical symptoms, including diarrhoea, dermatitis - a scaly rash over sun-exposed areas such as the neck, forearms, and hands, and dementia with features of disorientation, confusion, memory loss, and psychosis, constitute the syndrome known as Pellagra disease. Blood or tissue NAD levels can be used as a measure of niacin status. Other causes of niacin deficiency include

inadequate oral intake, poor bioavailability from grains, defective tryptophan absorption, carcinoid tumors, metabolic disorders, and the long-term use of chemotherapeutic treatments.

1.4. Vitamin B6 (pyridoxine)

The biologically active form of vitamin B6 is pyridoxal phosphate (PLP), a coenzyme for enzymatic reactions, primarily involved in amino acid metabolism and biosynthesis of heme and neurotransmitters [13]. PLP is the main coenzyme not only for the aminotransferases but also for the decarboxylases and various lyases and synthetases. Absorption occurs in the small bowel. After absorption, pyridoxine metabolites are phosphorylated and oxidised to pyridoxal phosphate in the liver, and are transported in plasma bound to albumin.

The RDA and DRI for ages 14–70 in both sexes is 1.3–1.7 mg/day [2]. Deficiency or lack of pyridoxine can cause a variety of diseases [14], including seborrheic dermatitis with cheilosis and glossitis, microcytic anemia, epileptiform convulsions, confusion, and/or depression and angular stomatitis.

Measurement should be done in presence of signs of pyridoxine (B6) deficiency. Vitamin B6 status should be determined by measuring plasma pyridoxal phosphate (PLP) levels. In seriously ill patients or in presence of inflammation, red cell PLP should be measured.

Populations with the greatest risk for deficiency include alcohol use disorder (AUD), renal dialysis patients (especially continuous renal replacement therapy), the elderly, post-operative (surgical process), infections, critical illness, pregnancy and people receiving medical therapies that inhibit vitamin activity (i.e., isoniazid, penicillamine, anti-cancer, corticosteroids, and/or anticonvulsants) [7].

1.5. Vitamin B9 (folate)

Folate refers to a family of molecules including natural and synthetic forms (folic acid), nutritional sources of folate include legumes and pulses (200–300 g cover RDA) and leafy green vegetables (400 g cover RDA); eggs, nuts, and whole grain products also contain folate [7]. Folic acid is manufactured synthetically and converted in the body into its active form, tetrahydrofolic acid (THF), by reduction with NADPH. Food folates have a lower bioavailability compared to synthetic folic acid: the dietary folate equivalent (DFE) is defined as 1 mg of food folate, which is equivalent to 0.6 mg folic acid from fortified food, or a supplement consumed with food (which equals 0.5 mg of a folic acid supplement taken on an empty stomach or given intravenously). Symptoms of folate deficiency overlap with vitamin B12 deficiency, therefore, both vitamins should be assessed during the diagnostic procedure as there is an intricate interplay between the two vitamins.

Folate plays a pivotal role in the production of DNA/RNA and metabolism of amino acids. It decreases the likelihood of neural tube defects in newborns when administered to women planning to become pregnant [15].

Folates are absorbed in the small intestine and vitamin C improves its bioavailability. For the general healthy population, the DRI (DFE) is 250–400 mg daily, with pregnant women approximately twice as much [16]. Parenteral nutrition should deliver 400–600 mg folic acid per day, enteral nutrition should provide 330–400 mg DFE per day in 1500 kcal.

Folate status may be conventionally assessed by measuring levels of folate in serum/plasma and reflect recent dietary folate intake. Red blood cell folate level is a more sensitive marker of long-term folate status during the preceding 3 months. Isolated folate deficiency is rare in developed countries, but an increased risk is known – among others - in severe alcohol abuse, poor nutrition, chronic kidney disease, in methotrexate use and post bariatric surgery.

There is no known toxicity for folic acid, excess is excreted in the urine, but the Lowest Adverse Effect Level (LOAEL) is set at 5 mg/day.

In macrocytic anaemia or malnutrition, folic acid status and vitamin B12 should be measured at least once and repeated within a few months after supplementation to verify normalization.

1.6. Vitamin B12 (cobalamin)

Cobalamin is a general term for cobalt containing vitamin B_{12} compounds. It is an essential water-soluble MN synthesized by fungi and microorganisms, and in the stomach of ruminant animals dependent on soil cobalt content [17].

Cobalamin absorption consists of several steps: after its release from proteins under the action of gastric acid and pepsin, followed by binding to R-protein produced by the salivary glands, it binds to the gastric intrinsic factor. These steps are followed by the absorption of intrinsic factor–cobalamin complexes in the terminal ileum. Degradation of R protein in the small intestine allows binding to gastric produced intrinsic factor and uptake by the ileal mucosa [18]. In adults the cobalamin reserves, which are stored mainly in the liver, will last for approximately 12–36 months without sufficient intake [17].

Cobalamin is a cofactor for two enzymes in humans: methionine synthase in methyl transfer from methyl tetrahydrofolate to form methionine from homocysteine; and methyl malonyl-CoA mutase in synthesis of the citric acid cycle intermediate succinyl CoA [17]. These pathways are essential for mitochondrial metabolism, immune response, preservation of DNA integrity, and of the myelin sheath around neurones, and synthesis of neurotransmitters participating in normal blood cell formation as well as neurological functions [18].

Vitamin B12 deficiency can cause a multitude of signs or symptoms: hematological (macrocytic anaemia, fatigue, weakness, shortness of breath, pancytopenia), neurological (peripheral neuropathy, paresthesia, sensory loss of extremities, tingling, numbness, vertigo, demyelisation of corticospinal tract and dorsal columns-ataxia), neuropsychiatric (irritability, mood-disorders/mood-swings, psychosis, depression), cognitive (malaise, fatigue, weakness) or glossitis. Cobalamin deficiency should be excluded in all patients who present with anemia, or isolated macrocytosis, established diagnosis of polyneuropathies, neurodegenerative diseases, or psychosis.

Inadequate intake is the main cause of low serum cobalamin in younger adults and likely the main cause in poor populations worldwide: it is caused by low consumption of animal-source foods. Intestinal malabsorption explains numerous cases of cobalamin deficiency. Absorption of cobalamin from food requires normal stomach, pancreas, and small intestine function: intestinal resection or reconstruction are therefore at high risk of causing deficiency. The most prevalent causes of deficiency are the autoimmune condition known as pernicious anemia, resulting from lack of intrinsic factor and, food-bound cobalamin malabsorption. Both conditions are also common with chronic atrophic gastritis, which affects around 10–30% of people over 60 years. Long term treatment of diabetes with metformin exposes numerous patients to deficiency risk.

In all patients at risk, or on treatment with cobalamin, replenishment adequacy should be assessed at least annually by resolution of clinical symptoms and available laboratory markers.

Adult patients at risk or suspected of cobalamin deficiency should be screened with the combination of at least two

biomarkers (holo-transcobalamin, and methylmalonic acid); serum cobalamin being a surrogate biomarker.

1.7. Vitamin B7 (biotin)

Biotin can be found in all cells of the human body. It plays an important role in the metabolism of fatty acids, glucose, and amino acids as it is a cofactor for carboxylase enzymes. Biotin is also a regulator of gene expression and affects the functions of adaptive immune T and NK cells [19]. Biotin sufficiency is essential for normal fetal development. In cell turnover, biotin is released by the action of biotinidase, which is also involved in release of the protein-bound biotin in the diet. Most biotin is absorbed in the small intestine, but some may also be synthesised by gut microflora and absorbed in the colon.

The European Food Safety Authority (EFSA) recommends an adequate intake of 40 μg/day for healthy adults [20]. The main biotin sources in Western countries are egg yolks, milk, yeast, some organ meats, and multi-vitamin supplements.

Biotin deficiency is rare in the general population due to its wide availability. Biotin deficiency leads to dermal (i. e. dermatitis, alopecia) as well as neurological complications such as ataxia [21]. Conditions at risk of developing deficiency include chronic alcohol consumption, malabsorption in the context of Crohn's disease and colitis, short bowel syndrome, celiac disease, severe malnutrition, smoking, and pregnancy. Long-term antibiotic use may destroy bacteria that produce biotin.

Biotin status may be assessed in presence of clinical symptoms suggesting biotin deficiency and a history suggestive of inadequate intake. Biotin status should be determined by the direct measure of blood and urine biotin and should be completed by the determination of biotinidinase activity.

1.8. Vitamin C (ascorbic acid)

Vitamin C comprises both ascorbic acid and its oxidized form dehydroascorbic acid. All its biochemical functions are based on electron donation. In humans, vitamin C is the primary circulating antioxidant, and it is also important for regeneration of other antioxidants, alpha-tocopherol, and glutathione. Furthermore, vitamin C improves immune function and wound healing, and acts as cofactor in the synthesis of catecholamines, cortisol and carnitine [22].

The recommended DRI of vitamin C in healthy individuals is 90–100 mg per day. Ascorbic acid is well absorbed in the small intestine. It exists in the plasma in the free reduced form and is readily taken up into cells. Excess amounts of ascorbic acid are excreted in the urine [23].

Deficiency of vitamin C leads to scurvy, which has multiple clinical features, including petechiae, bruising, inflamed and bleeding gums, arthralgia, and impaired wound healing. Hemodynamic consequences may present as pulmonary hypertension [24]. Pathognomonic of scurvy are corkscrew hairs. Less severe deficiency may present as gingival inflammation and fatigue. In infants there may be impaired bone growth and ossification [23].

Assessment of vitamin C status consists of direct measurement, either of plasma vitamin C for recent intake, or leukocyte vitamin C for whole body assessment. Cigarette smoking significantly lowers plasma vitamin C due to increased turnover and current recommendations are for higher intakes in such individuals. In patients with inflammation plasma concentrations can be substantially decreased due to redistribution (apparent deficiency) but also due to increased metabolic use and losses by bodily fluids (real depletion) [7].

1.9. Vitamin A (retinol)

Vitamin A is a fat-soluble vitamin and a prohormone. From the precursor retinol two different active metabolites are formed: retinoic acid and retinal. Retinol and retinal are responsible for vision and reproductive function. Retinoic acid controls cellular growth and differentiation especially in mucous membranes [25]. Vitamin A also plays an important role in the immune system.

Fat-soluble micronutrients including vitamin A and carotenoids are assumed to follow the lipids in the gastrointestinal tract, and their absorption presumably occurs in the upper half of the small intestine. Vitamin A circulates in plasma bound to its specific carrier protein retinol binding protein (RBP), which is part of a larger complex together with prealbumin (transthyretin). RBP is a negative acute phase protein, which leads to a fall in serum retinol [26]. Inflammation also reduces absorption of vitamin A and increases requirement and urinary loss which together may contribute to the development of vitamin A deficiency [27].

For the vitamin A needs, the average demand is expressed in retinol activity equivalents (RAE). RAEs are based on the amount retinol and of carotenoids absorbed from food. The recommendations for adults are 700 mg RAE (women) and 900 mg RAE (men) per day [7]. Principal nutritional sources are liver, meat, fish, and dairy such as cheese and butter; vegetarian sources are sweet potatoes, carrots, beans, spinach, broccoli, and mango. In case of vitamin A intake below recommendation, the liver stores are sufficient to maintain functions for about 6 months.

Serum retinol and retinyl esters (if available) measurements should be considered in patients being investigated for malabsorption. Vitamin A status should be determined by measuring serum retinol. Serum/plasma retinol concentrations decrease with increasing inflammation [28].

Deficiency of vitamin A leads to night blindness due to insufficient rhodopsin synthesis, Bitot spots-grey/white, foamy appearance on the conjunctiva, and ultimately xerophthalmia. There is an increased susceptibility to infections, especially of the respiratory tract as the main symptom [29].

Deficiency should be sought in chronic liver disease, chronic alcohol consumption, chronic kidney disease, short bowel syndrome, and obesity. High retinol serum levels are often observed in patients with chronic kidney disease and therefore supplementation is not recommended at that time. This increase is only temporary if the liver stores become depleted and can lead to a vitamin A deficiency.

1.10. Vitamin D (calciferol)

In 1928, the Nobel prize for chemistry was awarded in 1928 to Adolf Windaus for his studies on vitamin D, a fat-soluble vitamin and a prohormone. Indeed, it is not a vitamin in the classic sense because cutaneous endogenous production is possible from cholesterol with UV-B exposure. Therefore, there is a strong seasonal variation in vitamin D (25(OH)D) levels in un-supplemented individuals. Vitamin D may also be obtained by nutrition (e.g. fatty fish, eggs), but this rarely covers the needs. Contrary to other vitamins, there is a specific vitamin D receptor (VDR) expressed in many body tissues, including skeletal and cardiac muscle, bone, immune cells and endocrine organs.

The active form of vitamin D3, calcitriol, 1α,25-dihydroxyvitamin D ($1,25(OH)_2D$), plays important roles in osteogenesis, calcium homeostasis, cellular differentiation, and immune responses.

Vitamin D has classic effects on bone and mineral (calcium, phosphorus) metabolism, acting on the target organs bone, intestine, and kidneys. Vitamin D also has non-classic pleiotropic effects.

Vitamin D has recently become the subject of strong interest and has been suggested to play a key role as a risk factor for cardiological diseases (CVD), including stroke, atherosclerosis, myocardial infarction (MI), and coronary artery disease (CAD), diabetes, various cancers, and reproductive health [30].

Vitamin D functions as a steroid hormone by the mechanism of its action directly on gene expression and is involved in the regulation of numerous genes.

Vitamin D deficiency is defined as a serum 25(OH)D concentration <50 nmol/L or 20 ng/ml. It affects about 40% of Europeans and severe deficiency (plasma concentration <30 nmol/L) is present in 13% [31]. The recommended daily oral intake (RDA) of vitamin D is 600–800 IU in adults [32], or 1500–4000 IU in patients "at risk for vitamin D deficiency" [32,33]. The upper daily limit for vitamin D intake is 4000 IU [32], but a higher upper limit of 10,000 IU for patients „at risk" for vitamin D deficiency has been suggested by the Endocrine Society [33]. Patients who need nutrition support are often vitamin D deficient and their need may be significantly higher. However, enteral nutrition products usually provides only 400 IU per day and parenteral multivitamin preparations typically include about 200 IU per ampoule.

Native vitamin D metabolites vitamin D3 (cholecalciferol) and vitamin D2 need to be differentiated from active 1,25 OH vitamin D forms such as calcitriol, the latter only being used in special circumstances such as severe chronic kidney disease or hypoparathyroidism.

Deficiency of vitamin D leads to impaired calcium absorption and secondary hyperparathyroidism, with rickets/osteomalacia being the classic severe vitamin D deficiency disease that is still prevalent today. There is also an increased susceptibility to infections, especially of the respiratory tract as the main symptom. Deficiency should be sought in chronic kidney and liver disease, as well as all malabsorptive states including post-bariatric surgery and obesity.

Vitamin D toxicity is possible but rare. Symptoms include hypercalcemia, hypercalciuria, dizziness and renal failure and are mediated by high calcium levels [34]. Toxicity is usually seen with deliberate or accidental overdoses (typically single doses of millions IU or daily doses of >10,000 or even 100,000 IU), manufacturing errors, especially in unregulated formulations and in genetically determined increased vitamin D sensitivity (i.e. CYP24A1 loss of function mutations, or idiopathic infantile hypercalcemia) [35].

1.11. Vitamin E (tocopherol)

Vitamin E comprises eight naturally occurring forms, but only the alpha forms are maintained in human plasma – tocopherols have a ring system with a long-saturated side chain whereas tocotrienols have an unsaturated side chain. Vitamin E supplements are esters of α-tocopherol [7].

Vitamin E is the most important fat-soluble antioxidant [36]. Its universal presence in cell membranes protects against lipid peroxidation induced by oxidative stress.

Vitamin E is relatively poorly absorbed and depends upon adequate micelle formation and uptake into enterocytes, and chylomicron production and absorption. Chylomicron remnants containing vitamin E are taken up by the liver, and vitamin E is then released into the circulation within very low-density lipoproteins. Vitamin E rapidly transfers between lipoproteins and tissue lipids.

Deficiency is rare in humans but may appear in severe malnutrition and patients with fat malabsorption e.g. short bowel or coeliac disease. The main signs are peripheral neuropathy, ataxia, skeletal myopathy, and pigmented retinopathy.

Vitamin E status is determined by the quantification of α-tocopherol in blood plasma or serum. Plasma α-tocopherol is positively correlated with lipoproteins and cholesterol; therefore, it is recommended to express vitamin E levels as lipid ratio (α-tocopherol/cholesterol) [36]. Plasma levels can be readily measured, but their relationship to intake is not clear, although plasma concentration may be suitable to confirm a very low intake.

1.12. Vitamin K

Vitamin K consists of two main families of lipid-soluble compounds, each based on substituted naphthoquinones; phylloquinones (K1), the plant form, contain a phytyl group, and menaquinones (K2), of animal origin, produced by bacteria in the bowel [7]. Vitamin K2 is classified into various subtypes, of which the most significant are K2-4, K2-7 and K2-8, containing 4, 7 and 8 isoprenyl side chains [37]. In humans, anaerobes like *Escherichia coli* present in the large intestine synthesize long chain derivatives of menaquinones (MK-7 to MK-11).

Vitamin K1 is essential for gamma-carboxylation of glutamic acid residues in certain proteins – especially blood coagulation factors (proteins C, S, M, Z, factors VII, IX, X and prothrombin).

Vitamin K2 assists in the formation of bones while preventing calcium from deposition in blood vessels, protecting the arteries from stiffening and the kidney from stone formation by acting as a cofactor in the carboxylation of osteocalcin (ucOC) and matrix Gla protein (ucMGP). K2-7 is beneficial in managing bone loss because it upregulates osteoprotegerin which is a decoy receptor for RANK ligand (RANKL) thus inhibiting bone resorption.

Vitamin K1 is preferentially retained in the liver and rapidly excreted, whereas K2 acts within the liver and is transported into the circulation. As a result, VK2 is available to the whole body, including for reuse in the liver. Vitamin K2 needs as RDI are separate from those of vitamin K1.

Phylloquinone is absorbed from the diet as a component of chylomicrons and circulates in VLDL and LDL. The relative contribution to the total intake of menaquinones produced by bacteria is not known, but some exogenous vitamin K is usually required.

The adequate intake for vitamin K is 1 mg/kg body weight per day according to EFSA and 120 mg for male adults and 90 mg for female adults as recommended by the Institute of Medicine. Deficiency of vitamin K leads to hypoprothrombinaemia, an increase in prothrombin time, and increased bleeding. Other symptoms can be poor bone development, osteoporosis, and increased cardiovascular disease.

Vitamin K status is classically measured by prothrombin time, which is not a sensitive indicator. It may be suitable for diagnosis of gross deficiency, but increasingly plasma phylloquinone (vitamin K1) concentration and an estimate of undercarboxylated prothrombin or osteocalcin are used for research purposes. Vitamin K status is of most concern in patients with fat malabsorption, severe liver disease, malnutrition, use of non-absorbed antibiotics and treatment with anticoagulants (vitamin K antagonists), where high dose vitamin K intake may be necessary for correction of blood coagulation [7].

1.13. Vitamins – summary of influence of metabolic stress

Serious illness affects vitamin metabolism in several ways:

- Increased metabolic rate increases the requirement, especially for water-soluble vitamins as coenzymes for increased turnover of metabolic pathways.

– Increased oxidative metabolism leads to an increased production of ROS. This will lead to increased utilisation of antioxidant vitamins, especially vitamin E and vitamin C.
– There is an altered distribution of vitamins in body fluids. The concentration of many vitamins in plasma falls, partly because of the fall in carrier proteins e.g. vitamin A falls with the acute reduction in plasma concentration of retinol binding protein. Vitamin C concentration falls due to increased uptake into cells and increased metabolic consumption.
– There may be increased losses from the body e.g. water-soluble vitamins during renal dialysis or by bodily fluids.

1.14. Assessment of vitamin status in clinical practice

A laboratory assessment of vitamin status can be indicated to confirm clinical suspicion. Some tests are available either routinely, or for research purposes. However, it may take 1–2 weeks to receive the results since analyses are laborious and expensive. A wide range of tests may be available, and methods for intracellular (in erythrocytes or leucocytes) measurement of most vitamins, or of enzyme reactions involving them, makes these tests more specific than measurement in plasma alone [38]. The most used measurements are those for 25(OH)D, plasma vitamin B_{12}, or plasma or red cell folic acid concentration.

Any blood determination of vitamins should include a simultaneous determination of C-reactive protein (CRP) (see 2.6).

2. Vitamins in clinical nutrition

The provision of an adequate amount of trace elements and vitamins is an integral part of all nutrition therapy regimens by any route.

2.1. Individuals at risk of deficiency

By the time a patient commences nutritional support, he/she may already have developed a whole body depletion of one or more essential nutrients. The extent of this will depend on a number of factors:

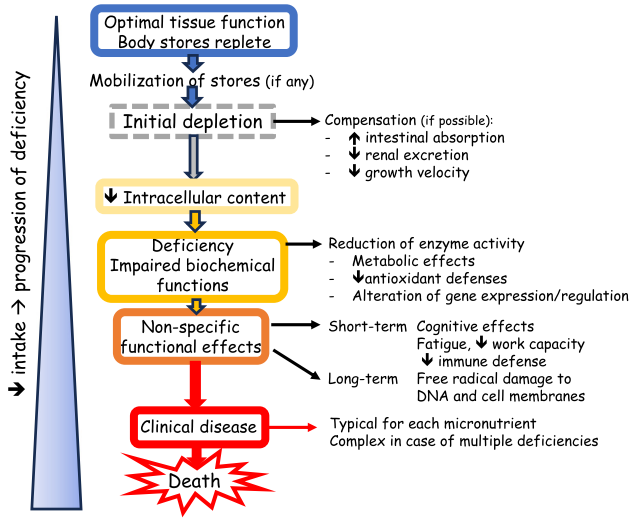

Fig. 1. With the progression of intake insufficiency, and depending on its magnitude, the consequences of intakes below DRI will first induce impaired biochemical functions that translate into clinically visible changes, and eventually death, with persistence and aggravation of the deficit.

– The nutritional state of the patient on admission to hospital. The pre-existing illness may have caused a period of anorexia, or inadequate digestion or absorption of nutrients.
– The duration and severity of inadequate nutritional intake whilst in hospital, as a result of surgery or other treatment.
– Any increased losses e.g dialysate fluid is rich in water soluble vitamins.
– Moreover, some individuals will have an increased daily requirement, partly to keep up with increased losses, and partly to meet metabolic requirements – these are particularly important when patients become anabolic after a period of catabolism or when normal growth resumes in a child.

Identification of potential micronutrient deficiencies should be part of the nutritional assessment of every patient, since conditions such as alcoholism, coeliac disease, inflammatory bowel disease, etc., predispose to such deficiencies. Students should make themselves familiar with the more common associations found in medical and surgical practice and be alert to their occurrence.

2.2. Clinical deficiency syndromes and sub-clinical deficiency states

»Classical « nutritional deficiency usually results in a complex syndrome of typical signs and symptoms, and these have now been fully characterized for each of the vitamins and trace elements. These syndromes were the basis on which the essential micronutrients were initially identified, and there is now a reasonable understanding of the nutritional consequences of severe deficiency, and the intake necessary to prevent clinically obvious deficiency from developing.

It is, however, now clear that as an individual develops progressively more severe depletion of one or more micronutrients, he/she will pass through a series of stages with biochemical or physiological consequences. The metabolic or physiological penalty of such a sub-optimal nutritional status is usually not clear, but the assumption remains that this impaired metabolism is likely to result in detrimental effects. Similarly, specific, and localized tissue deficiencies can occur which can lead to pathological changes. Such situations can be defined as sub-clinical deficiency. The time course for development of a sub-clinical deficiency state varies for each individual micronutrient and depends upon the nature and amount of tissue or body stores. The progressive consequences of an inadequate intake are more clearly delineated in Fig. 1.

A sub-clinical deficiency state can be either absolute or relative. Thus, an intake less than the requirement in normal health will lead to subclinical deficiency, or to a typical clinical deficiency state. However, certain patients have significantly increased requirements as a result of their disease process, and hence an intake normally regarded as adequate may be relatively insufficient and lead to a sub-clinical deficiency state. Most of the recommendations for vitamin and trace element supplements in total PN (TPN), and the content in enteral feeds, include an allowance for an increased requirement in disease.

2.3. Optimisation of vitamin provision

Defining the optimal intake of micronutrients is very difficult. It is possible to make a reasonable assessment of the requirements of an individual, based upon the requirements in health, the likely underlying nutritional state of the patient at the time of presentation, and the ongoing effects of the disease process. Such a level of provision using the enteral feeds and intravenous additives, which are currently commercially available, has been proved to be adequate in most cases to prevent the development of a deficiency state. However, provision of micronutrients to ensure the best possible tissue

Table 2
ESPEN Recommendations for daily trace element and vitamin intakes 2022 (all values are per day). Adapted from Table 15 from [7].

Vitamins	PN: Home and long-term PN A	PN with high requirements[a] B	EN In 1500 kcal[b] C	EN with high requirements in 1500 kcal[c]	DRI	EC directive[d]: Min - max per 1500 kcal [42]
Lipo-soluble						
A Retinol [e]	800–1100 μg	1100 μg	900–1500 μg	1500 μg	700–900 μg	525–2700 μg
D3 Cholecalciferol	200 IU/5 μg	800–1000 IU/20–25 μg	25 μg	30 μg	15–20 μg	7,5–37,5 μg
E α-tocopherol	9–10 mg	20 mg	15 mg	40 mg	15 mg	7.5–45 mg
K2 menaquinone	150 μg[f]	1–10 mg[g]	120 μg	Same as C	90–120 μg	52.5–300 μg
Water-soluble						
Vitamin B family	Provide **at least** [h]		Provide **at least** [h]			
B1 Thiamine	2.5 mg	100–200 mg	1.5 mg	100 mg	1.1–1.2 mg	0.9–7.5 mg
B2 Riboflavin	3.6 mg	10 mg	1.2 mg	10 mg	1.1–1.3 mg	1.2–7.5 mg
B3 Niacin	40 mg	Same as A	18 mg	40 mg	11–16 mg	13.5–45 mg
B6 Pyridoxine	4 mg	6 mg	1.5 mg	7.5 mg	1.5–1.7 mg	1.2–7.5 mg
B7 Biotin	60 μg	Same as A	30 μg	75 μg	30 μg (AI)	11.25–112.5 μg
B9 Folic acid	400 μg	600–1000 μg	330–400 μg DFE	500 μg	400 μg DFE	150–750 μg
B12 Cyancobalamin	5 μg	Same as A	>2.5 μg	7.5 μg	2.4 μg	1.05–10.5 μg
C Ascorbic acid	100–200 mg	200–500 mg	100 mg	200 mg	75–90 mg	33.75–330 mg

Abbreviations: EN = enteral nutrition, EC = European Council, PN = parenteral nutrition, AI = Adequate Intake, DFE = dietary folate equivalent. DRI = dietary reference intake.
[a] Increased requirements may occur in patients with on-going increased losses such as gastrointestinal losses, continuous renal replacement therapy, those who are hypermetabolic or who are depleted before commencing PN, and in pregnancy.
[b] The above recommendations for EN are formulated for 1500 kcal/day, which has been confusing for many as EN is often prescribed in millilitre. This concept aims at covering minimal requirements while delivering clinically realistic amounts of feeds. International surveys indicate this amount of energy as being the most commonly prescribed target, while the feed delivery is generally below, resulting in around 1000 kcal/day often delivered Since all the MN are incorporated in the EN formula, the amount of each MN supplied depends on the volume of feeds that are provided [42]. Table 3 provides examples of the amounts delivered using a common 1 kcal/ml EN product. The table shows the amounts of 13 vitamins and 4 trace elements according to the delivery of 3 levels of energy comparing them to the DRI and to the safe amounts according to the EC directive.
[c] Increased requirements during critical illness and in patients with acute admission with malnutrition (NRS 5): intended for max 15 days as repletion, to avoid requiring IV supply.
[d] The European Council (EC) directive regulates the contents of FSMP (Foods for Special Medical Purposes), [42]. Amounts are indicated per 100 kcal in the EC document. This column indicates the minimal and maximal trace element contents of such FSMP for 1500 kcal/day.
[e] Retinol includes retinol and retinyl ester.
[f] During PN, vitamin K requirements are usually provided by the lipid emulsions – status to be controlled in case of prolonged administration.
[g] High dose administered in case of coagulopathy (not nutrition-related.
[h] For water-soluble vitamins, the amounts recommended are minimum quantities, and more can usually be safely delivered.

Table 3
Amounts of MNs received by the patients depending on the quantity of energy delivery using a product "XYZ", provided as 500 ml bags (its MN content in 500 ml is shown in the 2nd column) – see LLL-44-1 for trace elements (some examples provided below). Values in blue-bold indicate that DRIs are not covered by this amount.

Micronutrient	„XYZ" MN content	Prescribed/received amount:			DRI for adults	EC directive [42]
	Bag 500 ml 1 kcal/ml	900 kcal	1500 kcal	1800 kcal		
Vit. A μg RE	350	**630**	1050	1260	700–900	525–2700
Vit. D μg	5	**9**	15	18	15–20	7,5–37,5
Vit. E mg TE	6,5	**11,7**	19,5	23,4	15	7,5 - 45
Vit. B1 (thiamin) mg	0,65	1,17	1,95	2,34	1.1–1.2	0.9–7.5
Vit. B2 (riboflavin) mg	0,85	1,53	2,55	3,06	1.1–1.3	1.2–7.5
Vit. B3 (niacin) mg	8	14,4	24	28,8	11–16	13.5–45
Vit B5 (pantothenic) mg	2,35	**4,23**	7,05	8,46	5	2.25–22.5
Vit. B6 (pyridoxine) mg	0,8	**1,4**	2,4	2,9	1.5–1.7	1.2–7.5
Vit B7 (biotin) μg	25	45	75	90	30	11.25–112.5
Vit. B12 (cyancobalamin) μg	1,35	2,4	4,1	4,9	2.4	1.05–10.5
Vit.B9 (folic acid) μg	133,5	**240**	401	481	400	150–750
Vit. C (ascorbic acid) mg	33,5	**60,3**	100,5	120,6	75–90	34–330
Vit. K (phylloquinone) μg	33,5	**60**	101	121	90–120	52.5–300
Copper mg	0,665	1,2	2,0	2,4	0,9	0.9–7.5
Iron mg	6,5	**11,7**	**19,5**	**23,4**	30	7.5–30
Selenium μg	33,5	60,3	100,5	120,6	55	37.5–150
Zinc mg	6	10,8	18,0	21,6	8–11	7.5–22.5

function remains poorly defined. Possible methods of trying to optimise provision in relation to function can be considered with respect to the antioxidant system, and the immune system.

In the last decade, well controlled clinical trials did not show significant beneficial effects of high-dose monotherapy of micronutrients in patients with increased inflammation and oxidative stress (Vitamin C [39], Vitamin D [40], Se [41]), so currently only coverage of basal needs is recommended. The increasing number of patients dependent on life-long TPN makes the long-term provision of adequate amounts of micronutrients an important part of nutritional therapy and requires monitoring of blood levels.

2.4. European legislation and ESPEN guidelines

The European Union has issued a directive on Dietary Foods for Special Medical Purposes (FSMPs) [42]. This includes guidelines on vitamin and trace element content of products. These values were integrated in the ESPEN micronutrient guideline published in 2022

[7], and its practical 2024 version [43]. The guideline provides information and recommendations for daily clinical nutrition practice regarding minimal MN doses to be delivered, assessment of micronutrient status, monitoring, and prescription. Main functions, optimal analytical methods, impact of inflammation, potential toxicity are described. Furthermore, recommendations for daily provision of both trace elements and vitamins during enteral or parenteral nutrition in at-risk diseases are given (see Table 2). This table also shows specific recommendations for patients with increased requirements, due to ongoing increased losses such as gastrointestinal losses, continuous renal replacement therapy, those who are hypermetabolic, in pregnancy, during critical illness and in patients with preadmission malnutrition.

Table 3 shows a practical example of micronutrient delivery using a typical commercial product (herein called "XYZ®): depending on the amount of energy presribed or delivered to a patient (900, 1500 or 1800 kcal), the same product, which has a fixed composition (see under "XYZ"), will cover partially (iron) or completely the DRI, and even modestly exceed them, but will never exceed the FSMP directive's maximal values.

2.5. Pharmaceutical aspects

Risk of toxicity: Although water-soluble vitamins are generally regarded as being virtually free of toxic effects when given in large amounts, fat soluble vitamins and trace elements have a much narrower range of safe yet adequate dosage. An excess of vitamin D provision not only causes hypercalcaemia, but it has also been linked to the metabolic bone disease of long-term TPN. Vitamin A toxicity has been observed during TPN in patients with renal failure. Vitamin E toxicity is extremely rare even after several years on TPN, even with the omega-3 PUFA emulsions that are enriched with vitamin E.

Drug interactions: Care must be taken to minimize interactions between nutrients, or between individual micronutrients and the infusion bags or giving sets. Minimizing the effects of artificial or daylight is important, especially for vitamins A and E. Protecting the bag and presence of fat emulsions minimises this effect. Chemical interaction with trace elements, especially the oxidative effect of copper on vitamin C is minimized by addition immediately before infusion. Oxidation of vitamins can be minimized by use of multilayered bags.

2.6. Assessment and monitoring in clinical practice

Some tests commonly used to assess vitamins are included in Table 1. The presence of inflammation in the context of surgery, trauma, infection or many acute or chronic diseases, complicates the assessment of the status based on blood levels. Using the surrogate CRP as a marker of its intensity, it has been clearly shown that inflammation induces a redistribution of many micronutrients from the circulating compartment to other organs, resulting in low levels for most micronutrients [28]. Low blood levels therefore do not necessarily indicate deficiency or even depletion. Therefore, CRP should be determined at the same time as any micronutrient analysis.

Acute vitamin deficiency occurring during nutritional support is rare, except if vitamins (such as riboflavin) are excluded from the micronutrient formulation. The non-administration of thiamine during parenteral nutrition may lead to thiamine deficiency. It is also important to consider that some vitamin deficiencies are frequently associated with other deficiencies (such as riboflavin deficiency is frequently associated with pyridoxine, folate, and niacin deficiencies).

In PN, vitamin A deficiency may occur in prolonged hypermetabolic conditions. Vitamin A is light sensitive [44] and may undergo photodegradation so light protecting material should be used during administration. It may also be lost by adsorption to infusion bags. In long-term parenteral nutrition these losses call for periodic monitoring. Similarly, vitamin C is unstable in parenteral nutrition, being rapidly oxidized according to first-order kinetics [45]. The degradation is based directly on the amount of oxygen present in the mixture, becoming relevant to the packing material, stimulated principally by high temperatures, and catalyzed by trace elements such as copper. Multilayered bags should be used, and light protection is mandatory.

As a general clinical practice, the laboratory tests which are available to assess vitamins are usually only used when there is a particular clinical problem where confirmation of micronutrient deficiency is necessary. If such tests are not available, and a deficiency is suspected, a therapeutic trial, especially of increased water-soluble vitamins can be safely given. In patients receiving enteral nutrition or parenteral nutrition where some intestinal absorptive capacity may still be present, an oral or enteral multimineral or vitamin supplement may also be provided. Alternatively, an increase in intravenous supply can be given for a limited period, with careful clinical monitoring.

3. Conclusion

The clinical manifestations of vitamins depletion and deficiency require time to develop and become visible but insufficient intakes compromise optimal metabolic functions as soon as they occur. Ensuring the delivery of the DRI amounts of vitamins (and trace elements) is the first step of a comprehensive nutritional therapy, but it is not sufficient as the different diseases may generate specific higher needs, and the individual patients have different metabolic requirements. It is therefore essential during medical nutrition therapy, to monitor the real delivery of nutrients and their blood levels (or the linked biomarkers) to ensure an optimal management of the individual patient.

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Declaration of competing interest

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