

# Water and Electrolytes in Health and Disease

Topic 2

## Module 2.2

### Vitamins

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#### Learning Objectives

- To list the vitamins which need to be supplied to patients receiving artificial nutrition
- To know the effects of deficiency of vitamins
- To understand the reasons why patients receiving artificial nutrition may have increased requirements
- To understand the value and limitations of methods of assessing status in patients receiving nutritional support

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### **Key messages**

- Vitamins are an essential part of all diets, both in normal individuals and in those requiring nutritional support;
- Patients requiring intravenous nutrition should receive vitamins from the beginning of their intravenous nutrition (IV);
- Requirements in disease are often greater than in health, to cope with increased metabolic requirements and increased losses;
- Optimising intake of vitamins in nutritional support is difficult since laboratory tests are rarely sufficiently sensitive and specific in patients with an inflammatory response.

## **1. Vitamins- biochemical function, effects of deficiency and methods of assessment**

This is a large field, and the reader is referred to textbooks of nutrition(1), and to recent issues of the Dietary Reference Intakes from the USA(2-4) for a more detailed discussion.

### **1.1 Thiamine (vitamin B<sub>1</sub>)**

Thiamine, usually in the form of thiamine pyrophosphate functions in the metabolism of carbohydrates and branched chain amino acids. It is absorbed mainly in the jejunum, and is transported in the blood in plasma and erythrocytes.

Clinical signs of deficiency are widespread, initially with anorexia and weight loss, mental changes and muscle weakness. Severe deficiency has a number of clinical presentations:

- Wet beri-beri, with cardiac failure and oedema;
- Dry beri-beri with neurological changes and muscle weakness;
- Shoshin beri-beri is a fulminant cardiac failure with severe lactic acidosis, sometimes seen in intensive care units.

Metabolic stress as a result of severe illness acutely increases the need for thiamine, as a result of increased oxidative metabolism and increased carbohydrate provision in the diet.

Thiamine status is best assessed clinically, supported by measurements of erythrocyte thiamine, or the effect of added thiamine on erythrocyte transketolase activity in vitro.

### **1.2 Riboflavin (vitamin B<sub>2</sub>)**

Riboflavin is an integral part of the co-enzymes flavine mononucleotide (FMN) and flavine – adenine dinucleotide (FAD) – it is therefore a catalyst for redox reactions throughout metabolic pathways.

Riboflavin is absorbed from the gut after hydrolysis of the bound co-enzymes. It circulates bound to albumin and immunoglobulins, and is converted to active co-enzyme within the cytoplasm of most tissues. Excess riboflavin is excreted in the urine.

Signs of deficiency include cheilosis, angular stomatitis and glossitis and a seborrheic dermatitis.

There is assumed to be a link with energy intake and therefore also with increased metabolism in stress. The best test for riboflavin status is erythrocyte riboflavin, or the activation in vitro of erythrocyte glutathione reductase.

### **1.3 Niacin**

Niacin (nicotinamide or nicotinic acid) has a central role in redox reactions, either as a hydride acceptor or donor, as part of the co-enzymes nicotinamide adenine dinucleotide (NAD), or its phosphate (NADP). These are of special importance in both carbohydrate and fat metabolism, and are synthesised in all tissues of the body. Excess niacin is excreted in the urine, mainly in the form of N-methyl-nicotinamide.

Severe niacin deficiency gives rise to pellagra, which has a typical symmetrical pigmented rash, a bright red tongue, gastrointestinal upsets, depression and memory loss. It would be unusual to measure niacin status, due to the complexity of tests, which include urinary excretion of metabolites, plasma concentration, or erythrocyte NAD.

Metabolic stress is assumed to increase niacin requirement and recommendations for niacin intake are usually linked to those for energy intake.

### **1.4 Vitamin B<sub>6</sub>**

Vitamin B<sub>6</sub> consists of pyridoxine and related compounds, the most metabolically active in man being pyridoxal phosphate (PLP). It is a co-enzyme for a large number of enzymes, primarily involved in amino acid metabolism. After absorption, pyridoxine metabolites are phosphorylated in the liver, and are transported in plasma bound to albumin. Excess pyridoxine is largely excreted in urine in the form of 4-pyridoxic acid.

Deficiency of vitamin B<sub>6</sub> leads to seborrhoeic dermatitis, and to a microcytic anaemia as a result of decreased haemoglobin synthesis.

Serious illness leads to increased protein and amino acid turnover – this will lead to an increased requirement for pyridoxine.

The best markers of PLP status are plasma PLP that reflects the tissue stores of PLP, especially in the liver, but its concentration is subject to the effects of the acute phase response on plasma albumin. Alternatively, erythrocyte amino transferase has been widely used.

### **1.5 Folate**

Folate is the term used to describe a group of vitamins related to folic acid. Folic acid itself rarely occurs in food, but is the form used in nutritional supplements. Food folate contains 1-6 additional glutamate residues.

Folate co-enzymes take part in many reactions involving 1-carbon transfers, nucleic acid synthesis and amino acid inter-conversions. Food folates are hydrolysed to monoglutamate (folic acid) before absorption. Circulating folate is either free or bound to low affinity protein binders, especially albumin. For activity as a co-enzyme, folate monoglutamate must be converted intracellularly to polyglutamate forms.

Folate deficiency leads to a rise in homocysteine concentration due to interference of the pathway, which regenerates methionine from homocysteine. Elevated homocysteine is currently recognised as being an independent risk marker for coronary artery disease. There is much current interest in the potential beneficial effect of reducing homocysteine concentration by increasing folate intake. Clinical effects of folate deficiency include megaloblastic changes in bone marrow due to failure of DNA synthesis, leading to macrocytic anaemia.

The best markers of folate status are erythrocyte folate, which reflects whole body folate status, plasma homocysteine (which is a sensitive but non-specific marker), with plasma folate being regarded as an indicator of recent folate intake.

### **1.6 Vitamin B<sub>12</sub>**

Cobalamin is a general term for cobalt containing vitamin B<sub>12</sub> compounds. The main commercial form is cyanocobalamin. The active forms in the body are coenzymes methylcobalamin or 5-deoxyadenosyl cobalamin, which are cofactors, especially for methyl transfer from methyltetrahydrofolate to homocysteine.

Vitamin B<sub>12</sub> absorption is a complex process. This involves dissociation of B<sub>12</sub> from proteins in the stomach, complexing in the small intestine of B<sub>12</sub> to Intrinsic factor, which has been secreted from the stomach, and absorption via specific receptors in the terminal ileum. Approximately 50% of dietary vitamin B<sub>12</sub> is absorbed in the healthy adult and B<sub>12</sub> ultimately is excreted in the urine or in the bile. B<sub>12</sub> circulates in the plasma bound to transcobalamin.

Deficiency of vitamin B<sub>12</sub> gives rise to two clinical presentations. Pernicious anaemia is a macrocytic anaemia, similar to folate deficiency and results from failure of DNA synthesis. There may also be neutropenia and thrombocytopenia. Neurological changes on the other hand may include sensory disturbances especially in the lower limbs, gait abnormalities,

memory loss and disorientation. About 25% of cases may only have neurological changes. The haematological changes are fully reversible although neurological changes may not.

The best estimate of B<sub>12</sub> status is serum B<sub>12</sub> concentration. Metabolic markers of increased methylmalonic acid and homocysteine in serum may be helpful but lack specificity.

### **1.7 Biotin**

Biotin is a cofactor for carboxylase enzymes, mainly present in mitochondria. 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.

Deficiency of biotin has been observed in clinical nutrition and is characterised by dermatitis, conjunctivitis, alopecia and other abnormalities of the central nervous system. Plasma biotin is rarely measured and is a poor marker. The best markers of biotin status are decreased urinary biotin excretion, and increased urinary 3-hydroxyvaleric acid, which accumulates as a result of decreased enzyme activity.

### **1.8 Vitamin C**

Vitamin C comprises both ascorbic acid and dehydroascorbic acid (DHA). The most important biochemical function is to act as a reducing agent – as a cofactor for certain metalloenzymes, especially those involved in collagen hydroxylation, and as an aqueous phase antioxidant. It is also important for regeneration of other antioxidants, alpha-tocopherol and glutathione.

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.

Deficiency of vitamin C leads to scurvy, which has multiple clinical features, including petechiae, bruising, inflamed and bleeding gums, arthralgia and impaired wound healing. Less severe deficiency may present as gingival inflammation and fatigue. In infants there may be impaired bone growth and ossification.

Assessment of vitamin C status consists of a range of functional measures as well as direct analysis. Functional measures include markers of oxidative damage of polyunsaturated fatty acids and DNA, and the extent to which these can be improved by vitamin C supplements. Greater specificity can be derived from 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. Although there is some theoretical evidence for increased requirement in exercise or metabolic stress, there is little direct evidence of benefit. However plasma concentrations fall rapidly after surgery or in infection due to increased uptake by tissues.

### **1.9 Vitamin A**

Vitamin A is a fat-soluble vitamin comprising a family of complex 20-carbon molecules (retinol, retinal, retinoic acid). The term vitamin A includes pro-vitamin A carotenoids which are present in the diet and are converted to vitamin A in the intestinal mucosa after absorption.

Vitamin A has a number of roles – for transduction of light into neural signals, to ensure normal structure of the cornea, and to maintain epithelial cell structure and function. Retinoic acid is a key regulator of gene expression for structural proteins, and has immune enhancing properties.

Vitamin A is absorbed as retinol during the absorption of fats in chylomicrons, and partly as retinoic acid directly to the liver bound to albumin.

Deficiency of vitamin A leads to xerophthalmia, a condition that passes through stages of increasing severity: - night blindness, conjunctival dryness, local damage (Bitot's spots), corneal ulceration and scarring, and finally blindness.

The best marker for assessment of vitamin A status is dark adaptation. Plasma vitamin A concentration correlates poorly with vitamin A stores and the concentration is also affected by changes in plasma retinol-binding protein, which is affected by protein and zinc status, as well as by the acute phase reaction. Renal failure leads to high plasma vitamin A concentration due to reduced losses in the urine.

### 1.10 Vitamin D

Vitamin D exists in two main forms:

- Cholecalciferol (vitamin D<sub>3</sub>) is the main form in man, being synthesised in the skin under the action of ultraviolet light.
- Ergocalciferol (vitamin D<sub>2</sub>) is the main form ingested in the diet, primarily from plants.

Neither form is biologically active until it is converted in the liver to the 25-OH derivative, and this to the 1,25(OH)<sub>2</sub> derivative in the kidney.

1,25(OH)<sub>2</sub> vitamin D is the active form of the vitamin, and it controls plasma calcium concentration by modulating calcium absorption from the small intestine, phosphate excretion in the kidney and calcium release from bone. Vitamin D may also have other effects not related to calcium metabolism.

Vitamin D deficiency is characterised by osteomalacia, where there is a defect in mineralisation of bone matrix, pseudofractures may occur causing bone pain, and there may be psychological changes such as depression, and a proximal neuromyopathy. There is a risk of bony fracture following minimal trauma.

The best assessment of vitamin D status is measurement of plasma 25-OH vitamin D, assuming renal function is normal. In addition, measurement of serum calcium, alkaline phosphatase and parathyroid hormone will give a good indication of the control of calcium metabolism.

In severe disease or organ failure, vitamin D metabolism may be markedly affected. Either liver failure or kidney failure may prevent hydroxylation of vitamin D, so that the active form is not produced, leading to a fall in serum calcium. Severe gastrointestinal disease with diarrhoea may lead to a loss of magnesium, causing reduced secretion of parathyroid hormone, in turn leading to reduced 1,25-OH vitamin D production and a fall in serum calcium.

### 1.11 Vitamin E

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 alpha tocopherol.

Vitamin E functions as a non-specific chain breaking antioxidant. This prevents propagation of free radical reactions, especially in polyunsaturated fatty acids in membrane lipids and plasma lipoproteins.

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. The main signs are peripheral neuropathy, ataxia, skeletal myopathy and pigmented retinopathy.

Assessment of vitamin E status includes biomarkers of resistance to haemolysis using hydrogen peroxide, or an increase in lipid peroxidation. Plasma vitamin E can be readily measured, but its relationship to intake is not clear, although plasma concentration may be suitable to confirm a very low intake. Vitamin E status is particularly affected in situations where there is fat malabsorption e.g. short bowel or coeliac disease.

### **1.12 Vitamin K**

Vitamin K consists of two main families of compounds, each based on substituted naphthoquinones; phyloquinones, the plant form, contain a phytyl group, and menaquinones, produced by bacteria in the bowel contain polyisoprenyl side chains.

Vitamin K is essential for gamma-carboxylation of glutamic acid residues in certain proteins, especially blood coagulation factors. Osteocalcin and matrix-Gla protein in bone also require vitamin K for gamma carboxylation to achieve optimal function.

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.

Deficiency of vitamin K leads to hypoprothrombinaemia, an increase in prothombin time, and increased bleeding.

Vitamin K status is classically measured by prothombin time, but this is not a sensitive indicator. It may be suitable for diagnosis of gross deficiency, but increasingly plasma phyloquinone concentration and an estimate of under carboxylated prothombin or osteocalcin are used for research purposes. Vitamin K status is of most concern in patients with severe liver disease, where high dose vitamin K intake may be necessary for production of blood coagulation factors, or where a low intake is coupled with the use of non-absorbed antibiotics, leading to reduced gut derived vitamin K.

### **1.13 Vitamins - summary of influence of metabolic stress**

Serious illness affects vitamin metabolism in a number of ways:

- Increased metabolic rate increases the requirement, especially for water-soluble vitamins as co-enzymes for increased turnover of metabolic pathways.
- Increased oxidative metabolism leads to an increased production of reactive oxidant species (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.
- There may be increased losses from the body e.g. water soluble vitamins during renal dialysis.

### **1.14 Assessment of vitamin status in clinical practice**

A laboratory assessment of vitamin status is rarely required. Some tests are available either routinely, or for research purposes. A wide range of tests may be available, and methods for intracellular measurement of most vitamins, or of enzyme reactions involving them, makes these tests more specific than measurement in plasma alone<sup>5</sup>. The most commonly used measurements are those for 25-hydroxy vitamin D, plasma vitamin B<sub>12</sub>, or plasma or red cell folic acid concentration.

### **1.15 Summary**

Vitamins are essential organic micronutrients, which are required in the diet in relatively small amounts. However, they are essential both for maintenance of health and treatment of disease. The function of vitamins and their deficiency states are summarised in Table 1

**Table 1.** Vitamins - Functions, biochemical model of action, effects of deficiency and methods of assessment. Modified from(6)

|                                   | Function(s)                                                               | Biochemical modes of action                                                | Effects of deficiency                                                                          | Assessment of Status                                                                  | Comments                                                                           |
|-----------------------------------|---------------------------------------------------------------------------|----------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|
| <b>Vitamin A</b>                  | Visual acuity<br>Antioxidant<br>Growth and development<br>Immune function | Rhodopsin in retina<br>Free radical scavenger<br>Induces DNA transcription | Xerophthalmia<br>Night blindness<br>Increased risk of some neoplasms                           | Plasma retinol<br>Plasma retinol binding protein                                      | Fall in retinol during acute phase response due to fall in retinol binding protein |
| <b>Vitamin D</b>                  | Calcium absorption<br>Differentiation of macrophages                      | Receptor mediated transcription                                            | Osteomalacia (adults)<br>Rickets (children)<br>Immune status ↓                                 | Serum Ca/P/alkaline phosphatase<br>Serum 25-OH vit D ,<br>1,25(OH) <sub>2</sub> vit D |                                                                                    |
| <b>Vitamin E</b>                  | Antioxidant in membranes                                                  | Free radical scavenger                                                     | Haemolytic anaemia<br>Atherosclerosis<br>Certain neoplasia                                     | Plasma tocopherol/ cholesterol                                                        | Vitamin E is transported in LDL.                                                   |
| <b>Vitamin K</b>                  | Blood coagulation<br>Bone calcification                                   | α-glutamyl carboxylation<br>Coagulation proteins and osteocalcin           | Bleeding disorders.<br>? Bone disorders.                                                       | Prothrombin time.<br>Plasma phylloquinone                                             | Time consuming assay                                                               |
| <b>B<sub>1</sub> (thiamine)</b>   | Carbohydrate and fat metabolism                                           | Decarboxylation reactions as TPP                                           | Beri-beri with neurological cardiac effects<br>Wernicke-Korsakoff Syndrome<br>Immune function↓ | RBC transketolase                                                                     | Deficiency may occur and is reversed rapidly                                       |
| <b>B<sub>2</sub> (riboflavin)</b> | Oxidative metabolism                                                      | Coenzyme as FAD or FMN                                                     | Lesions of lips, tongue, skin<br>Possibly immune function↓                                     | RBC glutathione reductase                                                             |                                                                                    |
| <b>B<sub>6</sub> (pyridoxine)</b> | Amino acid metabolism                                                     | Trans-amination reactions                                                  | Anaemia (children)<br>Lesions of lips and skin<br>Premenstrual symptoms                        | RBC transaminase                                                                      |                                                                                    |
| <b>Niacin</b>                     | Oxidative metabolism.                                                     | Coenzyme as NAD/NADP.                                                      | Pellagra-rash, weakness, diarrhoea                                                             | Urine N - methyl nicotinamide                                                         | Rarely measured                                                                    |

|                                  |                                                                 |                                                                                                  |                                                                                        |                                   |                                              |
|----------------------------------|-----------------------------------------------------------------|--------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|-----------------------------------|----------------------------------------------|
| <b>B<sub>12</sub></b>            | DNA metabolism.                                                 | Recycling folate coenzymes<br>Valine metabolism                                                  | Megaloblastic anaemia<br>Demyelination of neurones                                     | Serum Vitamin B <sub>12</sub>     |                                              |
| <b>Folate</b>                    | Purine/ pyrimidine metabolism                                   | Single carbon transfer                                                                           | Megaloblastic anaemia                                                                  | Serum folate<br>RBC folate        | Recent intake<br>Whole body status           |
| <b>Biotin</b>                    | Lipogenesis/ gluconeogenesis                                    | Carboxylase reactions                                                                            | Scaly dermatitis<br>Hair loss                                                          | Serum biotin<br>Urine biotin      | Rarely assayed                               |
| <b>Vitamin C (ascorbic acid)</b> | Collagen synthesis<br><br>Antioxidant<br><br>Absorption of iron | OH proline/ OH lysine synthesis<br><br>Reduction reactions<br>Fe <sup>+++</sup> Fe <sup>++</sup> | Scurvy. Impaired wound healing<br><br>Impaired immune function<br><br>Oxidative damage | Leucocyte Vit C.<br>Plasma Vit C. | Plasma vitamin falls in injury or infection. |

## 2. Vitamins in clinical nutrition

### 2.1 Introduction

The provision of an adequate amount of trace elements and vitamins is an integral part of all nutrition support regimens by both parenteral and enteral routes.

### 2.2 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:

- 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.

### 2.3 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 consequences of an inadequate intake are more clearly delineated in Figure 1:

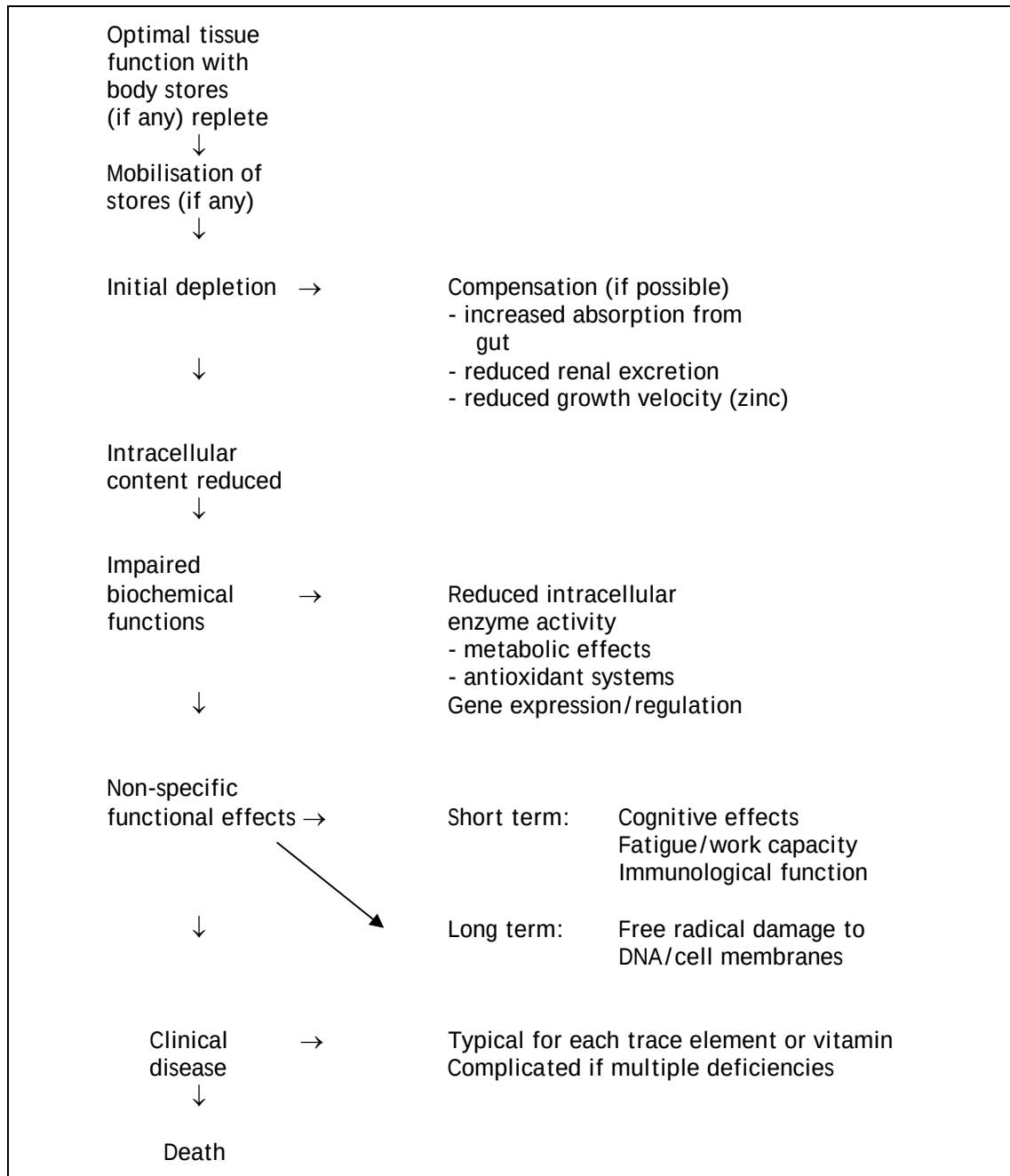


Fig. 1 Consequences of inadequate micronutrient intake

A sub-clinical deficiency state can be either absolute or relative. Thus an intake less than the requirement in normal health will lead to sub-clinical 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 TPN, and the content in enteral feeds, include an allowance for an increased requirement in disease.

## **2.4 Optimisation of provision of vitamins**

Defining the optimal intake of micronutrients is far from ideal. 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 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 also to the immune system.

It is to be expected that in the next few years, well controlled clinical trials will help to clarify the situations where increased provision of these micronutrients is or is not helpful, both in reducing the biochemical effects of reactive oxidant species (ROS), and also in altering complication rates and outcome in serious illness. Many of the disease states thought to be associated with ROS are chronic degenerative conditions, such as atherosclerosis and neoplastic disease. 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.

## **2.5 European Union Legislation and Enteral Nutrition**

The European Union has issued a directive on Dietary Foods for Special Medical Purposes (FSMPS). This includes guidelines on vitamin and trace element content. In many cases, the minimum intake suggested for an individual with an energy intake of 2000 kcals is in excess of the reference intake in a normal population. This allows for the increased requirement of most individuals receiving enteral nutrition. The directive defines FSMPS as

- *nutritionally complete standard formula* – which can be used as a sole source of nutrition – these must comply with the guidelines for micronutrient composition, as shown in table 2 .
- *nutritionally complete, nutrient adapted disease specific formula* – which also must be suitable as a sole source of nutrition.
- *nutritionally incomplete formulas* – which are not suitable as a sole source of nutrition.

Selection of the most appropriate tube feed often requires assistance from an experienced dietician. Students should be aware that although the micronutrient composition must lie within the ranges quoted, these are wide and they have been designed for a 2000 Kcal intake, which is rarely achieved enterally. Different commercial products can have quite different amounts of micronutrients. 1500 kcals of feed is an intake, which is more widely met in clinical practice. The range of amounts present in this amount of feeds, which are currently available in Europe, is therefore also shown as a guide in table 2

## **2.6 Vitamins in enteral and parenteral nutrition**

A summary of suggested intravenous and enteral intakes of vitamins in nutritional support is provided in Table 2

**Table 2** Vitamins in parenteral and enteral nutrition

|                                   | Units | IV Supplement                         |                  | Enteral Nutrition |         |                                                        |
|-----------------------------------|-------|---------------------------------------|------------------|-------------------|---------|--------------------------------------------------------|
|                                   |       | Vitalipid N<br>+<br>Solivito N<br>(1) | Cernevite<br>(2) | EC Directive      |         | Approx amount<br>(3) in feed<br>providing 1500<br>kcal |
|                                   |       |                                       |                  | Minimum           | Maximum |                                                        |
| <b>A (retinol)</b>                | µg    | 1000                                  | 1000             | 700               | 3600    | 770-2100                                               |
| <b>D (cholecalciferol)</b>        | µg    | 5                                     | 5.5              | 10                | 50      | 10-12                                                  |
| <b>E (α tocopherol)</b>           | mg    | 10                                    | 10.2             | 10                | 60      | 18-36                                                  |
| <b>K</b>                          | µg    | 150                                   | -                | 70                | 400     | 80-150                                                 |
| <b>B<sub>1</sub> (thiamine)</b>   | mg    | 3                                     | 3.5              | 1.2               | 10      | 2.2-2.9                                                |
| <b>B<sub>2</sub> (riboflavin)</b> | mg    | 3.6                                   | 4.1              | 1.6               | 10      | 2.4-3.9                                                |
| <b>B<sub>6</sub> (pyridoxine)</b> | mg    | 4.0                                   | 4.5              | 1.6               | 10      | 2.5-4.0                                                |
| <b>Niacin</b>                     | mg    | 40                                    | 46               | 18                | 60      | 25-30                                                  |
| <b>B<sub>12</sub></b>             | µg    | 50                                    | 6                | 1.4               | 14      | 3-6                                                    |
| <b>Folate</b>                     | µg    | 400                                   | 414              | 200               | 1000    | ~400                                                   |
| <b>Biotin</b>                     | µg    | 60                                    | 69               | 15                | 150     | 60-75                                                  |
| <b>C (ascorbic acid)</b>          | mg    | 100                                   | 125              | 45                | 440     | 100-150                                                |

1. Fresenius-Kabi
2. Baxter Health Care
3. Various commercially available standard feeds

### **2.6.1 Risk of toxicity of vitamins**

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.

### **2.6.2 Pharmaceutical aspects of provision of vitamins and trace elements in intravenous nutrition**

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.

### **2.7 Assessment and monitoring in clinical practice**

Some tests commonly used to assess vitamins are included in Table 1. The acute phase reaction associated with trauma and infection markedly affects plasma concentration of many vitamins, reducing the plasma concentration of virtually all water soluble and fat soluble vitamins.

Because of the limitations in interpretation of these data, it is common practice, especially in patients receiving TPN, only to assess folic acid on a regular basis, and possibly vitamin D in those on long term nutritional support. The other 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 TPN where some intestinal absorptive capacity may still be present, an oral or enteral multi-mineral or vitamin supplement may also be provided.

A two-week course of a well balanced micronutrient supplement is unlikely to cause any harm, and may occasionally be beneficial. Alternatively, an increase in intravenous supply can be given for a limited period, with careful clinical monitoring. In such cases a blood/plasma sample at the beginning of supplementation should be stored for possible analysis at a later date.

### **3. Summary**

Vitamins are an essential component of nutritional support, with key roles in metabolic pathways and as antioxidants. This module summarises some of the effects of vitamin deficiency, the limited role of the laboratory in assessing status, and makes recommendations for supply.

### **References.**

1. Shils ME, Olson JA, Shike M, Ross AC. Modern Nutrition in Health and Disease. 9th ed. Baltimore: Williams and Wilkins; 1999
2. Food and Nutrition Board IoM. Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids. Washington, DC: National Academy Press; 2000
3. Food and Nutrition Board IoM. Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin, and Choline. Washington, DC: National Academy Press; 1998.
4. Food and Nutrition Board IoM. Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc. Washington, DC: National Academy Press; 2002.
5. Sauberlich HE. Laboratory Tests for the Assessment of Nutritional Status. 2nd ed. Boca Raton, FL: CRC Press; 1999.

6. Shenkin A. Adult micronutrient requirements. In: Payne-James J, Grimble G, Silk D, editors. Artificial Nutrition Support in Clinical Practice. 2nd ed. London: GMM; 2001. 193-212.1.