Assessment and interpretation of vitamin and trace element status in sick children. A position paper from the ESPGHAN Committee in Nutrition

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* Anthony Catchpole is a guest to the Committee of Nutrition invited for the purposes of this position paper

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What is known

- In routine clinical practice, measurement of vitamin and trace element (VTE) concentrations in blood or in other biological fluids is the mainstream approach to evaluate body status.
- In disease and particularly in conditions associated with systemic inflammatory response, interpretation of VTE concentrations in blood, as markers of body status, can be challenging and potentially mislead clinical practice.
- Evaluation of adequacy of body status of VTE using solely dietary assessment methodology can be inaccurate and imprecise, particularly in disease and in assessment per individual.

What is new

- The use of a multimodal approach, including clinical examination, dietary assessment and biomarkers, is the optimal way to ascertain the VTE status of individual patients.
- CRP and serum albumin should be measured alongside plasma VTE concentrations, particularly where the disease state may result in a systemic inflammatory response.
- Assessment of blood measurements of VTE should be best performed in the absence of systemic inflammatory response and should be interpreted in the context of the clinical condition and history.

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Abstract

Assessment of vitamin and trace element status (VTE) is important in the clinical management of the sick child. In this position paper we present the various assessment methods available to the clinical practitioner, and critically discuss pitfalls with interpretation of their results.

There are four main approaches to assess the VTE body status of an individual patient including clinical examination, dietary assessment and measurement of direct and indirect biomarkers of VTE in biological samples. Clinical signs of VTE deficiencies usually present only when body stores are substantially depleted and are often difficult to detect or differentiate from other non-nutrient related causes. In isolation, dietary assessment of micronutrients can be inaccurate and imprecise, in disease and in individual patient assessment, but may be useful to complement findings from other VTE assessment methods. Use of biomarkers is the most common approach to assess VTE status in routine practice, but in the presence of systemic inflammatory response and in the absence of appropriate paediatric reference intervals, interpretation of biomarker results might be challenging and potentially mislead clinical practice.

The use of a multimodal approach, including clinical examination, dietary assessment and laboratory biomarkers is proposed as the optimal way to ascertain the VTE status of individual patients. In the presence of acute inflammatory conditions, VTE measurements in plasma should be replaced by biomarkers not affected by systemic inflammatory response or delayed until inflammatory state is resolved.

Introduction

Vitamins and essential trace elements (VTE) are micronutrients which are important enzyme co-factors and co-enzymes, antioxidants and gene transcription factors(1) (Table 1). Vitamins have diverse biochemical functions within the human body, including energy production, regulation of gene expression, cellular growth and differentiation, organ and immune function(1-3). Trace elements are inorganic substances which are involved in enzymatic systems, antioxidant defence and other crucial metabolic pathways within the body. Adequate dietary intake of VTE is critical, as deficiencies are associated with a number of specific and non-specific symptoms which lead to loss of body homeostasis and function, and disease onset(3). In addition to a suboptimal dietary intake, the aetiology of VTE deficiencies in disease can be multifactorial and include malabsorption, excessive losses, increased requirements and drug-nutrient interactions(1-7).

There is continued interest in the role of the VTE, both from a public health point of view to prevent disease, and from a clinical practice perspective to monitor and treat deficiencies and optimise clinical outcomes. This interest stems from our increasing understanding of the biological roles of these nutrients, findings from nutritional epidemiology and the public interest in the potential health promoting benefits of these nutrients(8), as these may be portrayed to them by the commercial manufacturers of such supplements. A prime example of is the high prevalence on vitamin D in healthy and sick people of all ages and the implications this may(9) for public health and clinical practice, respectively.

It is, however, a common finding that research hypotheses generated from observational or epidemiological studies(10) are not confirmed by supplementation intervention studies aiming to normalize VTE biomarkers or suboptimal intakes(11, 12). Counterintuitive findings like these are rather disappointing and might be explained by other factors which confound the relationship between the levels of a VTE and health or clinical outcomes. Several studies may have also used inappropriate or inadequate methodology to assess the VTE status of a patient or population. It is

therefore of utmost importance for the nutrition researcher and health care professional to understand the various methodologies and limitations relevant to the assessment of body VTE status. For clinical practice, there are five fundamental reasons why assessment of VTE is important:

1) To confirm the clinical manifestation of deficiencies or toxicity in patients.
2) To screen and identify patients at risk of deficiencies or toxicity and refer them for diagnostic assessment.
3) To prevent under or over-supplementation and the possible effects on health and disease.
4) To supplement and potentially improve the clinical outcomes of patients with acute or chronic illness.
5) To reduce health care costs from unnecessary usage of resources to assess VTE status and from unnecessary interventions to correct non-existing deficiencies.

This position paper presents the various approaches available to health professionals to assess the VTE status in sick children. We critically discuss their validity and limitations in their use and make recommendations for routine clinical paediatric practice. This paper does not aim to present methods to assess VTE status of large populations as part of public health research. However, we acknowledge the importance of nutritional epidemiology in developing dietary intake standards and reference intervals for VTE biomarkers. Likewise, this position paper does not aim to retrieve and critically appraise all available literature on the topic, as this is rather broad and beyond its scope which is to raise awareness among health professionals regarding the assessment and interpretation of VTE status, using an evidence-based approach. We preferred not to label groups in which routine VTE assessment should be performed. Instead we leave this decision to the discretion of the health professional and in the context of the clinical scenario each time. This position paper does not discuss micronutrient supplementation either. Although the evidence and debate presented in this paper might also be applicable for minerals (inorganic micronutrients which are

required in much higher amounts than trace elements in our diet) this position paper focuses on VTE.

In order to retrieve micronutrient references developed specifically in children, and pertinent to the scope of this position paper, a literature search was carried out in Pubmed using the following terms and Boolean operators; *(micronutrient* [TIAB] OR vitamin* [TIAB] OR "trace element*" [TIAB]) AND (references [TIAB] OR intervals [TIAB] OR ranges [TIAB]) AND (child [TIAB] OR children [TIAB] OR paediatric [TIAB] OR pediatric [TIAB])*. Term search was restricted to abstract and title content only and literature published in English language only. Of the 494 search hits, 54 were screened as relevant based on title screening; 12 were included in the respective sections of this position paper. Leading articles of research carried out in adult participants were also included.

Assessment of body VTE status

There are three main approaches (Figure 1) to assess the VTE status of an individual in-vivo.

a) Clinical examination of symptoms associated with the presence of VTE deficiencies.
b) Dietary assessment of VTE intake.
c) Laboratory biomarkers in biological fluids or tissues including:
    I. Direct measurements of the concentration of a VTE, its derivative or its binding protein.
    II. Functional tests including metabolic products, enzymatic activities or hormones for which a VTE acts as co-enzyme or co-factor.

Clinical examination of VTE deficiencies

In clinical examination the health practitioner looks for abnormal clinical and physical stigmata, in visible regions of the body (skin, nails, hair, eyes, oral cavity) that can be affected by nutrient unavailability. Presence of lesions, changes in colour, shape and texture can indicate VTE deficiencies(13, 14). There are several guides published with practical advice and steps on how to perform clinical examination for VTE deficiencies, which is beyond the scope of this position paper(13).

Clinical signs of VTE deficiencies usually present when body stores are substantially depleted; hence they are insensitive markers to indicate early deterioration of a patient's VTE body stores or subclinical deficiencies. Certain clinical signs are specific to a single or very few VTE, such as rickets in vitamin D deficiency, but other VTE deficiency signs are unspecific and often difficult to distinguish from non-nutrient related factors and conditions (Figure 1). It is therefore important to confirm findings from nutrition-associated clinical assessment with laboratory biomarkers and dietary assessment as these described below. Monitoring and evaluation of clinical signs at follow-up will confirm the initial diagnosis but also determine whether any intervention applied corrects the nutrition-related problem.

Assessment of dietary intake of VTE

Principles of dietary assessment

Adequacy of body VTE status using dietary assessment methods is often applied in nutritional epidemiology and in clinical research, and is advocated by professional bodies for use in routine practice(15, 16). However, this approach comes with several limitations (Figure 1). It assumes that a nutrient intake above a certain dietary reference value provides the needs of the body. As with the assessment of macronutrients, such as protein, carbohydrate and fat, assessing VTE status with dietary assessment methods assumes that nutrient absorption, metabolism and loss are comparable

to those of healthy people, upon whom the dietary references values have been developed. Such assumptions may be invalid to make for conditions where the physiological dynamics of nutrient metabolism have been altered or bypassed. A prime example is the onset of cytopaenia, secondary to copper deficiency, in children receiving exclusive jejunal feeding(17), faecal loss of fat soluble vitamins in children with cystic fibrosis and pancreatic insufficiency(18), and antagonism of folate metabolism in children receiving immunosuppression with methotrexate(19).

Dietary reference values

Several countries worldwide have developed dietary reference values for VTE using various methodologies. Most of these dietary reference values have been based on observed intakes in the healthy population, occasionally with the inclusion of detailed nutrient balance studies, for infants based on the nutrient content of breastmilk with mathematical extrapolations for older ages, and the intake needed to maintain a desirable level of a nutrient, nutrient-dependent proteins or enzymatic reactions in biological samples. Few properly performed VTE balance studies exist. For instance, the European Food Safety Authority (EFSA) has set the dietary reference values of copper for adults and children based on mean observed intakes in several European Union countries where there is no evidence of overt copper deficiency(20). For selenium these are based on the concentration above which there is levelling-off of plasma selenoprotein P concentration, a functional marker reflecting saturation of the functional selenium body pool, and for iodine using urinary excretion and data on the incidence of goitre from nutritional surveys in European school-aged children(20, 21). In all cases, dietary reference values have been set for the intake of each VTE below which the likelihood of a deficiency state is increasing. At their set levels the dietary reference values for VTE cover the requirements of 97.5% of the individuals within a population and they serve as the basis for dietary assessment and diet planning. For sick children, inflated adjustments for VTE are often applied to account for disease effects on VTE requirements, although several of these adjustments are based on theoretical premises. An alternative approach to establish optimal dietary

reference values for VTE might be to explore predictive relationships between micronutrient intakes and health outcomes such as growth and risk of disease onset in nutritional epidemiology. Dietary reference values encompass a broad umbrella of terms and quantitative reference values established to describe the nutrient intakes for populations and individuals and the reader is referred to the technical report issued by EFSA(20). The terminology used for dietary reference values, their basis and set thresholds varies among countries.

Dietary assessment methodology

Dietary assessment is generally only useful in assessing the VTE status of a patient when dietary intake data are collected accurately. This typically requires trained nutrition specialists or dietitians. There are several caveats to consider with the use of dietary assessment methods to estimate intakes of VTE (Figure 1). Methods developed to describe nutrient intakes of very large population in nutritional epidemiology, such as food frequency questionnaires or 24-hour past recalls(22), at best provide mean group estimates and offer ranking, as opposed to an estimation of an individual patient's nutrient intake(23). Even when correct ranking of VTE intake is the desired outcome of interest, such methods present modest correlation coefficients, poor accuracy and unpredictable precision error at per subject assessment, when compared with more accurate dietary assessment methods and biomarkers(22, 24, 25). Therefore, it is often incorrect and misleading practice to use nutritional epidemiology tools (e.g. food frequency questionnaires) to estimate nutrient intakes of individuals or small groups of patients. Reference methods of dietary assessment, such as weighed food diaries may be more accurate methods to estimate VTE intake but require meticulous recording of weighed food over a long period of time (7 days or longer) to capture inter-daily variation in VTE intake. This increases participation burden, misreporting and participants often distort their regular dietary habits during the recording period(24). Furthermore, dietary analysis depends on the availability and completeness of food composition databases, meaning assessments using food which lack detailed nutritional composition data may underestimate VTE intakes. This might be

particularly important for medical foods used extensively in the dietary management of children with chronic illness, such as gluten free products in coeliac disease and low protein foods for the management of children with phenylketonuria(26). Analysis of dietary intakes is performed using proprietary dietary analysis software or other digital workflows, each of which uses national or international food composition tables such as the McCance & Widdowson food composition tables in the United Kingdom or the United States Department of Agriculture food composition data in the USA and elsewhere.

Dietary intake data should not be used in isolation to assess the VTE status of an individual but in conjunction to clinical and biochemical assessments (Figure 2). However, correlations between dietary intake and assessment using biomarkers are often poor(23, 27). International health professional associations recommend the routine dietary assessment of children with some chronic conditions(15, 16) using food diaries twice or more per year but as these are resource-demanding tasks and need specialist staff, it is imperative to first prove their usefulness in improving patient care and outcomes.

Biochemical markers of VTE status

Biomarkers of VTE status can be quantitatively measured in various biological matrices such as blood, urine, saliva, cells, hair, and nails. These are the most common methods in use in clinical practice and are divided into two major families of laboratory tests. The first includes direct measurements of the concentration of VTE or their derivatives and binding proteins in biological fluids. When a direct measurement of a VTE is not available or secondly when this is not a reliable marker of body VTE status, functional biomarkers may be used (Table 1). Functional biomarkers provide an indirect assessment of the adequacy of body VTE by measurement of a metabolite, enzymatic reaction activity, or a hormone, dependent to this VTE. They are often more informative

in assessing body status than direct measurements of VTE concentration in biological samples. Typical examples of functional markers of VTE deficiencies are diminished glutathione peroxidase activity in plasma or erythrocytes in the presence of selenium deficiency, diminished erythrocyte transketolase activity in thiamine deficiency, raised plasma levels of methyl malonic acid in B12 deficiency(2) and thyroid hormone dysfunction in iodine deficiency (Table 1). Measurements of VTE concentrations in erythrocytes are more representative of long-term or tissue stores as opposed to measurements in plasma which are influenced by recent changes in intake. A detailed description of available biomarkers and laboratory methodology to quantify VTE biomarkers has been described extensively elsewhere(2, 14) and a summary is presented in Table 1. Although biochemical markers are often considered the reference method to ascertain body VTE status, there are various limitations regarding their use and interpretation, as presented in the following sections (Figure 1).

VTE reference intervals

Development of blood VTE reference intervals relies often on the 95% confidence intervals of the distribution of measurements in a population(28). In adults, robust blood VTE reference intervals exist but their availability in paediatric patients is scarce and often adult standards are adopted or adapted for use, often considering hypothetical demands for growth and biological variation with age, increasing the risk of over or under-identification of VTE deficiencies. In contrast to the WHO growth centile charts which describe the optimal pattern of growth for children rather than the prevailing pattern in a population, and account also for biological variation with gender and sex, there are very few similar age-dependent standards for VTEs in children(29-35). Hence definition of different VTE ranges across childhood is often arbitrarily determined and they do not follow the biological variation that some of these nutrients may have with age. To date, very few VTE balance studies using stable isotopes have been performed.

Several of the paediatric references used in health services and biochemistry laboratories are derived from small convenience samples of essentially healthy children recruited from the general population(36) or rely on inpatient or outpatient samples, and hence are likely to be unrepresentative of the distribution of the biomarkers in the population(37). Moreover, development of VTE reference intervals based on population distribution data in areas where VTE deficiency is a public health concern(38-40), may mask cases of true deficiencies and underestimate the proportion of subjects which need supplementation or nutritional support. The Canadian Laboratory Initiative on Pediatric Reference Intervals (CALIPER) has recently published paediatric reference intervals using robust methodology but these are limited to Vit A, Vit B12, Vit D, Vit E, folate, and serum caeruloplasmin (as a functional marker of copper) (37). Until high quality, internationally-agreed references are developed, clinical practitioners should use their local laboratory VTE reference intervals but taking also into consideration the issues highlighted in this paper.

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Effect of illness and inflammatory response

Suboptimal intake is perhaps the main cause of low circulating levels in healthy individuals. In illness, the systemic inflammatory response co-ordinates a sequence of biochemical reactions and physiological changes with the likely aim of limiting damage and aiding repair and recovery. In humans, a highly complex system regulates redistribution of VTE which ensures that there is an optimal concentration of each VTE in the tissue or body fluid at the various phases of the illness(41). The mechanisms behind these effects are multiple and many remain poorly understood. Among them is redistribution between tissues and body fluid compartments, changes in synthesis and loss of nutrient-carrier protein, including serum albumin and lipoproteins, as well as increased urinary excretion(3). As a result of these inevitable effects, the blood concentration of several VTEs will be affected, regardless of the actual body stores (Table 2).

A substantial amount of research to date shows that acute and chronic illness will affect blood VTE concentrations assayed in plasma, but those measured in erythrocytes remain relatively unaffected or not affected at all(42-44). The prime studies to demonstrate this are observational studies in patients admitted for elective surgery and followed-up during their recovery phase(42, 45, 46). As these patients are very likely to be nutritionally replete and do not receive specialised nutritional support during hospital admission, any changes in VTE concentrations are likely to be the result of the onset of systemic inflammatory response and recovery from it. The magnitude of systemic inflammatory response on plasma VTE concentrations was investigated in a large dataset of routine VTE screens(47) in Scotland and summarised recently in a systematic review(48). The effect size varies markedly from patient to patient, affects all VTE measured in plasma, both in acute and chronic illness, follows often a broad linear or exponential relationship between plasma nutrient concentration and inflammatory markers (e.g. CRP and serum albumin). The effect is greatest for selenium, zinc and the vitamins A, B6, D, and C, for which the median plasma concentrations can decrease by >40% (Table 2). For selenium and vitamins B6 and C, this effect occurs with only slightly increased C-reactive protein concentrations of 5 to 10 mg/L.

In general, most VTE concentration measurements are low and often below the reference intervals in patients with a systemic inflammatory response(48). Consequently, a reduction in concentrations is likely to result in an overestimation of a deficiency(49). In contrast, where the VTE biomarker is increased, as in the case of serum ferritin and caeruloplasmin concentrations, this may result in overestimation of iron and copper stores, respectively. With particular reference to copper, the systemic inflammatory response will decrease plasma concentrations in the short term (~24 hours post-insult), with significant increments following thereafter(42). The important implication of this evidence is that when a sick child has low plasma concentrations of a VTE it is difficult to differentiate between a true deficiency and an epiphenomenon. It has therefore been suggested that the concentration of the nutritional biomarker may reflect the activity of the disease, rather than the actual VTE status of a patient, in the presence of inflammatory response(41). It is currently

unclear whether low VTE levels, in the presence of systemic inflammatory response, can influence patients' outcomes or if VTE supplementation will improve or deteriorate these. In a study in adult patients in critical care, supplementation with B-complex vitamins did not affect their plasma levels(43) and a Cochrane meta-analysis of RCT of selenium supplementation found no effects on adverse clinical outcomes in critically adults(12). Likewise, a meta-analysis in patients with sepsis found no benefit of selenium supplementation on all-cause mortality, hospital-acquired pneumonia and length of intensive care unit stay(50). Similar findings have been reported in vitamin C administration in critically ill patients(51).

There have been substantial efforts to overcome the limitations of interpretation of body VTE concentration measurements in the presence of ongoing inflammatory response, but currently there is no accepted consensus. As several of the VTE circulate in the blood bound to nutrient-carrier proteins, a commonly used approach to account for the effect of the systemic inflammatory response is to correct for their plasma levels (Table 2). For example, vitamin K, which is transferred primarily bound to chylomicrons, will decline as a secondary effect of the acute phase response on lipoprotein metabolism(52). Plasma vitamin K concentrations are therefore unlikely to be a reliable measure of status during inflammation. Instead, the plasma vitamin K:triglyceride ratio(52) or other biomarkers such as the undercarboxylated serum vitamin K-dependent proteins (PIVKA-II)(53) provide more reliable measurement of vitamin K status. Similarly, as approximately 70% of plasma zinc is bound to albumin, zinc measurements in theory could be largely adjusted by albumin concentrations. This is not the case for selenium where >50% is bound to selenoprotein P and only 9% of plasma selenium is bound to albumin(54). The observation that the erythrocyte levels of certain VTE remain unaffected by the systemic inflammatory response(42-46) means that they have the potential to be used as surrogate biomarkers of VTE body stores for example as seen with the erythrocyte concentrations of selenium, B2 and B6(55) (Table 1). However, the same principle does not apply across all trace elements such as erythrocyte zinc. Analytical methods to measure VTE in erythrocytes or functional assays are not as available or widespread in routine clinical laboratories as

the direct measurements in plasma. The long half-life of the erythrocytes also limits the use of erythrocyte VTE biomarker concentrations for the assessment of acute deficiencies or recent supplementation(56).

Beyond the effect of the systemic inflammatory response on blood biomarkers, conditions affecting normal liver and renal function can perturb the concentration of VTE, regardless of actual body stores. Interpretation of blood micronutrient biomarkers may also be challenging in patients who received transfusions of blood products or certain drug therapy. In preterm infants, postnatal dexamethasone administration doubled retinol and retinol-binding protein independent of nutrient intake(57). Therefore, interpretation of biomarkers of VTE in blood should be done in the context of the clinical condition(29, 58).

Conclusion

This position paper provides a brief guide on available methods to assess micronutrient status in sick children at high risk of deficiencies (Table 3) and discusses pitfalls associated with interpretation of results of such assessments. The issues raised within this position paper need to be considered in routine clinical practice, and when appropriate, used to guide patient management, considering cost and resource availability.

Recommendations

Considering the currently available evidence, the Committee of Nutrition of ESPGHAN recommends

- Routine screening for VTE status is justifiable only in groups of patients with chronic conditions at high nutrition risk and in individuals on long-term exclusion diets. Clinical teams should conduct audit and adapt practice accordingly.

- VTE biomarkers should be interpreted in relation to the overall clinical condition and history of the individual patient.
- The use of a multimodal approach, including clinical examination, dietary assessment and biomarkers, including functional markers, is the optimal method to ascertain the VTE status of individual patients (Figure 2).
- Systemic markers of inflammation (e.g. CRP) and serum albumin should be measured alongside plasma VTE concentrations, particularly where the disease state may result in a systemic inflammatory response.
- Dietary assessment methods developed for use in nutritional epidemiology should not be used to diagnose VTE deficiencies in individual patients and especially in the absence of other methods.
- In the presence of inflammatory conditions, VTE measurements in plasma should be replaced by biomarkers not affected by the systemic inflammatory response or delayed until inflammatory state is resolved.
- Manufacturers of medical food products should be encouraged to provide data on the composition of all VTE.

Future research priorities

Considering the currently available evidence, the Committee of Nutrition of ESPGHAN recommends future research should focus on

- Development of robust paediatric VTE reference intervals for children using similar concepts as those adopted for the development of the optimal WHO growth charts and in the context of prediction of health outcomes in nutritional epidemiology.

- Discovery and validation of new biomarkers of VTE status that complement existing measures. There is a need for biomarkers which remain unaffected by the acute phase response and predict health outcomes.

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Figure Legends

Figure 1: Advantages and disadvantages of mainstream approaches to assess VTE status in paediatric patients

Figure 2: A decision tree to evaluate VTE status stores using laboratory biomarkers

DIETARY ASSESSMENT

Pros

- Non-invasive
- Detect early store depletion

Cons

- Inaccurate/imprecise in per subject estimations
- Prone to self-reporting bias
- Assumes same requirements as in health
- Time consuming
- Increase patient burden
- Incomplete food composition databases
- Needs dietitian
- Requires dietary analysis software

CLINICAL EXAMINATION

Pros

- Non-invasive
- Quick to perform

Cons

- Insensitive for early depletion
- Often unspecific
- Requires clinician with appropriate training

LABORATORY BIOMARKERS

Pros

- 'Objective' marker of body store adequacy
- Less prone to user error
- Assess current and long-term stores

Cons

- Often invasive
- Some need laborious assays
- Need specialised lab
- References intervals for children not always available
- Some reference intervals are based on selective populations
- Several affected by systemic inflammatory response
- Some affected by abnormal liver/kidney function

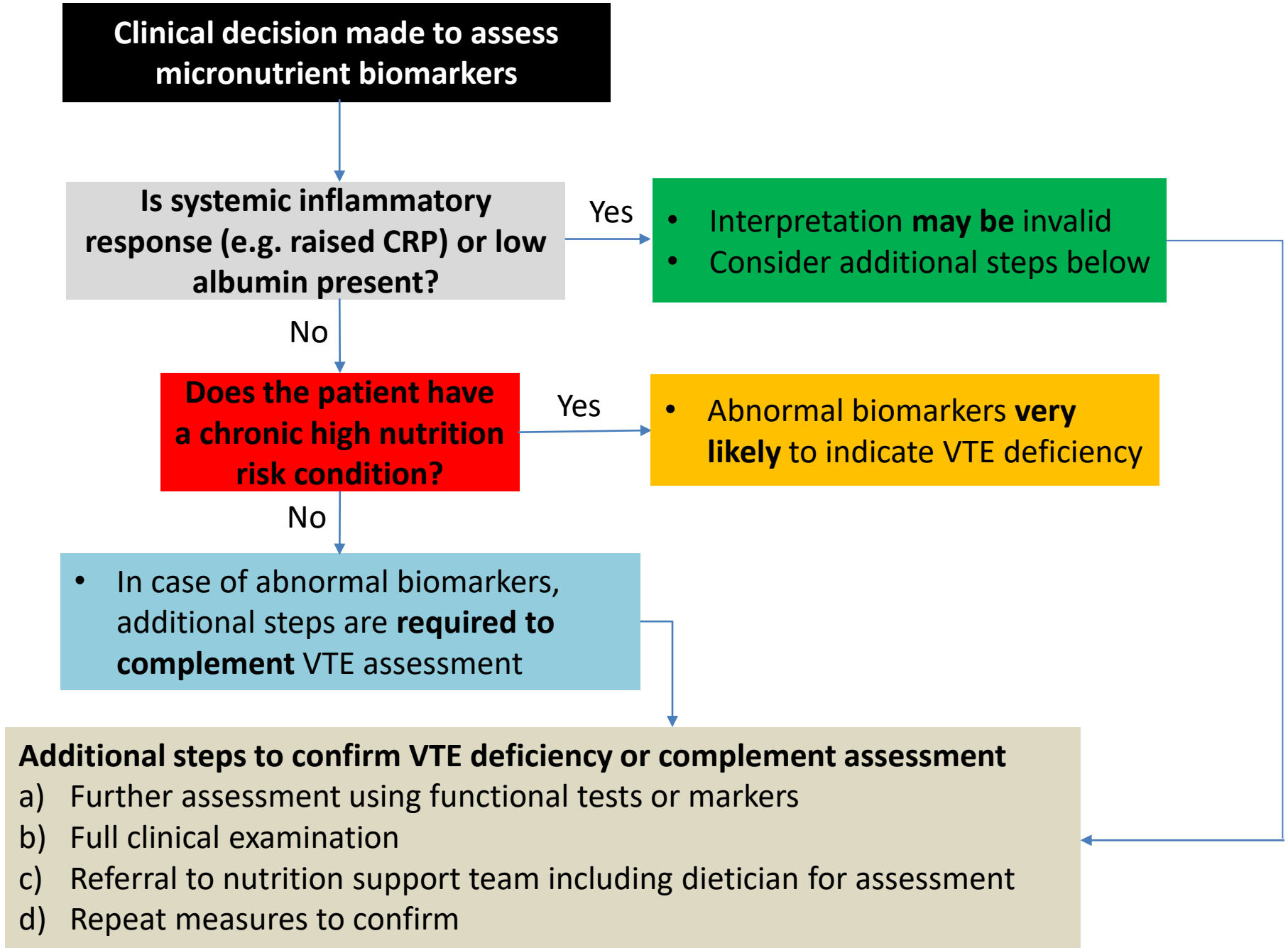
Clinical decision made to assess micronutrient biomarkers
Is systemic inflammatory response (e.g. raised CRP) or low albumin present?
Yes
• Interpretation **may be** invalid
• Consider additional steps below
No
Does the patient have a chronic high nutrition risk condition?
Yes
• Abnormal biomarkers **very likely** to indicate VTE deficiency
No
• In case of abnormal biomarkers, additional steps are **required to complement** VTE assessment
Additional steps to confirm VTE deficiency or complement assessment
a) Further assessment using functional tests or markers
b) Full clinical examination
c) Referral to nutrition support team including dietician for assessment
d) Repeat measures to confirm

Table 1: Direct and indirect biomarkers to assess VTE status

Micronutrient	Biomarkers	Biomarker unaffected by SIR	Suggested biomarker*
Trace element			
Se	• Plasma Se • RBC Se • Plasma selenoprotein P • Whole blood glutathione peroxidase • Plasma glutathione peroxidase • Selenium urinary excretion	• RBC Se • Whole blood glutathione peroxidase	• Plasma Se (in non-inflamed patients)
Zn	• Plasma Zn • Zinc urinary excretion		• Plasma Zn (in non-inflamed patients)
Cu	• Plasma Cu • Plasma caeruloplasmin • Copper urinary excretion		• Plasma Cu (in non-inflamed patients)
Fe	• Serum iron • Serum ferritin • Transferrin/total iron binding capacity • Transferrin saturation		• Serum ferritin (in non-inflamed patients)

	• Whole blood zinc protoporphyrin • Soluble transferrin receptors		
Mn	• Whole blood manganese • Plasma manganese		• Whole blood manganese
I	• Urinary iodine excretion • Plasma thyroid stimulating hormone • Plasma thyroglobulin		• Urinary iodine excretion (population marker)
Vitamins			
B1	• RBC thiamine diphosphate • Whole blood thiamine diphosphate • Erythrocyte transketolase activity	• RBC thiamine diphosphate • Whole blood thiamine diphosphate • Erythrocyte transketolase activity	• RBC or whole blood thiamine diphosphate (long term marker)
B2	• Plasma flavin adenine dinucleotide • RBC flavin adenine dinucleotide • Whole blood flavin adenine dinucleotide	• RBC flavin adenine dinucleotide • Whole blood flavin adenine dinucleotide	• RBC flavin adenine dinucleotide (long term marker)

	• Erythrocyte glutathione reductase activity		
B6	• Plasma pyridoxal 5'-phosphate • RBC pyridoxal 5'-phosphate* • Urinary pyridoxic acid • Kynurenine pathway metabolites	• RBC pyridoxal 5'-phosphate	• RBC pyridoxal 5'-phosphate (long term marker)
Folate	• Serum folate • RBC folate • Plasma homocysteine	• RBC folate	• Serum or RBC folate (long term marker)
Niacin	• Plasma niacin and derivatives • Niacin urinary excretion		• Plasma niacin and derivatives
Pantothenic acid	• Urinary pantothenic acid • Plasma pantothenic acid • Whole blood pantothenic acid		• Urinary pantothenic acid
Biotin	• Urinary biotin excretion • Urinary 3-hydroxyisovaleric acid		• Urinary biotin excretion

Vit B12	• Plasma B12 • Whole blood B12 • Holotranscobalamin • Plasma methylmalonic acid • Urinary methylmalonic acid • Plasma homocysteine		• Plasma vitamin B12
Vit C	• Plasma vitamin C		• Plasma vitamin C (in non-inflamed patients)
Vit A	• Plasma retinol • Plasma retinol binding protein • Changes in retinol binding protein following vitamin A administration		• Plasma retinol (in non-inflamed patients)
Vit E	• α tocopherol • α tocopherol/cholesterol	• α tocopherol/cholesterol	• α tocopherol/cholesterol
Vit D	• Plasma 25-hydroxy vitamin D		• Plasma 25-hydroxy vitamin D
Vit K	• Plasma phylloquinone	• Prothrombin time	• Plasma phylloquinone/triglycerides

• Plasma phylloquinone/triglycerides • Prothrombin time • Protein-induced in vitamin K absence-II	• Plasma phylloquinone/triglycerides

*Recommendations are made considering availability in diagnostic laboratories and current scientific evidence; SIR: Systemic inflammatory response

Table 2: Magnitude of the effect of systemic inflammatory response effect (% change) on plasma VTE concentration as reported in previous research (47)

Micronutrient	Lowest reported	Highest reported
Zinc	-10	-40
Selenium	-20	-65
Copper	10	15
Vitamin A	-10	-65
Vitamin D	0	-40
Vitamin E	0	-10
Vitamin B2	-10	-60
Vitamin B6	0	-70
Vitamin B12	0	-25
Vitamin C	0	-75
Lutein	-40	-75
Lycopene	0	-95
α-carotene	-20	-80
β-carotene	-20	-90

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Table 3: Indicative list of scenarios where screening for VTE might be considered*

Infants/children with clinical symptoms of malabsorption or protracted vomiting
Infants/children with established malnutrition/growth failure
Infants/children with multiple food allergies
Infants/children on long-term exclusion of major food groups (e.g. vegan, inherited disorders of metabolism)
Infants/children with major (e.g. >15%) unintentional weight loss
Infants/children on medication interfering with VTE metabolism (e.g. methotrexate)
Infants/children on long-term (>4 weeks) parenteral nutrition, particularly those on standard bags lacking certain essential VTE
Infants/children with pancreatic insufficiency (e.g. cystic fibrosis) with poor compliance on pancreatic replacement therapy
Infants/children on long-term post-pyloric feeding
Infants/children with refeeding syndrome
Infants/children with major burns
Infants/children with major resection of small intestine or high output stoma
Infants/children with severe insensible losses (e.g. severe skin disease as epidermolysis bullosa)
Infants/children with severe liver disease and cholestasis

*This is a non-exhaustive list of scenarios, but typical examples based on the consensus of the group. Decision to perform VTE assessment in these groups, as well as in other not presented here remain to the discretion of the health professional and within the context of the individual clinical case