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Review article

Revised reference values for the intake of thiamin (vitamin B_1), riboflavin (vitamin B_2), and niacin

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ABSTRACT

Background: The nutrition societies of Germany, Austria, and Switzerland are the joint editors of the 'reference values for nutrient intake'. They have revised the reference values for the intake of thiamin, riboflavin, and niacin and published them in February 2015.
Methods: All three vitamins have important functions as part of energy metabolism. Consequently, the reference values for the intake of these vitamins are derived in consideration of the reference values for energy intake (PAL 1.4).
Results: The reference values for infants aged 0 to under 4 months are derived from the nutrient content of breast milk. No data are available regarding thiamin, riboflavin, and niacin requirements for infants aged 4 to under 12 months, children, and adolescents. Therefore, the reference values for these age groups are based on the average requirement for adults and are calculated taking into account the age-based guiding values for energy intake (PAL 1.4) and assuming a coefficient of variation of 10%, due to the variation in requirement within the population. There are no data to suggest that the relationship between thiamin, riboflavin, niacin and energy requirement for pregnant and lactating women is any different from that for women who are not pregnant or not lactating.
Conclusion: Supplemental intake beyond the recommended amounts has no health benefit and is therefore not recommended.

Contents

1. Introduction

The D-A-CH 'reference values for nutrient intake' [1] are jointly issued by the nutrition societies of Germany, Austria, and Switzerland [the abbreviation D-A-CH stands for the initial letters of the common country identification for the countries Germany (D), Austria (A) and

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Switzerland (CH)]. Currently, the 'reference values for nutrient intake' are being revised. Following the revision of the reference values for vitamin D [2], calcium [3], folate [4], energy [5], selenium [6], and vitamin C [7] intake the revised reference values for thiamin, riboflavin, and niacin intake were published in February 2015.

Reference value is a collective term for recommended intake values, estimated values, and guiding values. A recommended intake value, according to its definition, meets the requirement of nearly any person (approximately 98%) of a defined group of healthy people. Estimated values are given when human requirements cannot be determined with desirable accuracy. Guiding values are stated in terms of aids for orientation [1].

The water-soluble B vitamins thiamin, riboflavin, and niacin have important functions as part of energy metabolism. Consequently, the reference values for the intake of these vitamins are derived in consideration of the reference values for energy intake [5].

In foods of animal origin, 95%–98% of *thiamin* is present in phosphorylated form, while thiamin in foods of plant origin is predominantly present as free thiamin [8]. In the human organism, thiamin diphosphate (TDP), also known as thiamin pyrophosphate (TPP), acts as a co-enzyme in important energy metabolism reactions. *Riboflavin* is a precursor of the co-enzymes flavin mononucleotide (FMN; riboflavin phosphate) and flavin adenine dinucleotide (FAD), which are components of oxidases and dehydrogenases [9].

Niacin is a general term for nicotinic acid (pyridine-3-carbonic acid) and nicotinamide (pyridine-3-carboxamide) as well as their derivatives. They are the basis for the formation of the pyridine nucleotides – nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP) – that act as co-enzymes[1]. Niacin is present in foods and formed in the human body in the liver from the essential amino acid tryptophan [10].

The niacin concentration in food as well as niacin intake and the reference values are specified in niacin equivalents (1 mg niacin equivalent = 1 mg niacin = 60 mg tryptophan) [11,12]. The amount of niacin equivalents is therefore calculated as niacin (mg) = nicotinamide (mg) + nicotinic acid (mg) + 1/60 tryptophan (mg) [13].

Since there is no evidence of adverse effects in humans, there are no tolerable upper intake levels given for thiamin and riboflavin [14,15]. For niacin, the US–American Institute of Medicine (IOM) defines age-dependent tolerable upper intake levels ranging from 10 mg/day for children up to 35 mg/day for adults [15]. The European Food Safety Authority (EFSA) differentiates between nicotinamide and nicotinic acid since nicotinamide rarely causes adverse effects compared to nicotinic acid in consequence of high intake. The tolerable upper intake levels for adults are 900 mg/day for nicotinamide and 10 mg/day for nicotinic acid [14].

2. Criteria for the assessment of the supply of thiamin, riboflavin, and niacin

Thiamin supply can be determined by measuring the transketolase activity in erythrocytes, which require TDP as a co-enzyme. The measurement of transketolase activity in erythrocytes is a functional parameter that is primarily used to assess thiamin supply [16]. TDP effects of >25% are defined as deficiency and effects between 15% and 25% as marginal deficiency [17].

Further status parameters used for the determination of thiamin supply are determination of TDP concentration in erythrocytes and measurement of thiamin excretion in urine [16,18].

Determination of erythrocytic TDP concentration is a sensitive detection method yielding similar results to the measurement of transketolase activity. A fall in TDP concentration in erythrocytes below 120 nmol/l indicates deficiency [16,18]. With regard to the measurement of the 24-hour urinary excretion of thiamin, excretion levels between 27 μg and 65 μg are defined as marginal deficiency and of <27 μg as deficiency [18]. This method only reflects the short-term supply and provides inadequate information on tissue reserves [16,18]. Thus, the determination of the transketolase activity and the TDP concentration in erythrocytes are preferred status parameters [17].

Riboflavin supply can be determined by measuring the glutathione reductase activity in erythrocytes, for which FAD is needed as a co-enzyme [16,19,20]. The activity coefficient is calculated from the ratio of enzyme activity with and without FAD addition. Activity coefficients of >1.4 indicate a riboflavin deficiency, while coefficients between 1.2 and 1.4 indicate a marginal deficiency [16]. In the case of a glucose-6-phosphate dehydrogenase deficiency, FAD increasingly binds to the glutathione reductase. As a consequence activity measurement of the enzyme can yield misleading results [19,21].

A further option for the determination of riboflavin supply is the measurement of urinary excretion of riboflavin. Riboflavin excretion in urine reflects the short-term supply [16,19,22] and correlates with riboflavin intake in people with a body nitrogen equilibrium [23]. 24-hour urinary excretion levels of riboflavin between 40 μg and 119 μg are defined as a marginal deficiency, with levels <40 μg being defined as a deficiency [16].

An activity coefficient of <1.2 and a 24-hour urinary excretion of riboflavin at a level ≥120 μg are considered as indicators for an adequate riboflavin supply [16].

Evaluation of *niacin supply* based on dietary intake of niacin equivalents is unreliable due to the differing bioavailability of niacin and its conversion from tryptophan, respectively. The intake of niacin equivalents correlates with the excretion of niacin metabolites in urine. Low excretion of the niacin metabolites N-methyl nicotinamide and N-methyl-2-pyridon-5-carboxamide indicates a low body store. Excretion of niacin metabolites in urine can therefore be seen as a marker of niacin supply [24–27]. Excretion of N-methyl nicotinamide and N-methyl-2-pyridon-5-carboxamide totalling less than 1.5 mg in 24 hours indicates a severe niacin deficiency [28]. As the concentration of N-methyl-2-pyridon-5-carboxamide declines to a higher degree than that of N-methyl nicotinamide as a result of reduced niacin intake, a ratio of less than 1.0 is a further indicator for niacin deficiency [10].

The concentration of niacin metabolites in plasma is less sensitive to changes in intake than the concentration in urine. Based on current knowledge, it is not possible to assess whether the concentration of niacin metabolites in plasma is suitable as a biomarker for niacin supply [29]. Inadequate supply can also be detected based on a decline in NAD concentration in erythrocytes [10]. There are contradictory findings with regard to the relevance of the ratio of NAD to NADP concentrations in whole blood for assessment of niacin supply [10,30].

3. Derivation of the reference values for thiamin, riboflavin, and niacin

3.1. Adults

For the derivation of the reference values for *thiamin* intake, studies primarily investigating the transketolase activity in erythrocytes, and also the excretion of thiamin in urine are used as a basis. A TDP effect of <15% and 24-hour urinary excretion levels of thiamin of >66 μg were taken as a basis for a target value for an adequate thiamin supply [17,19]. Using thiamin balance studies [31–33], the desired level of thiamin excretion in urine and adequate transketolase activity in erythrocytes was achieved given an intake of 0.45 mg thiamin/1000 kcal. This intake is specified as the average requirement [5].

For the derivation of the reference values for *riboflavin* intake, studies primarily investigating the glutathione reductase activity in erythrocytes and also the excretion of riboflavin in urine are used as a basis. An activity coefficient of <1.2 and a 24-hour urinary excretion level of riboflavin of ≥120 μg were taken as a basis for target levels [16]. Investigations

[1] NAD and NADP are abbreviations for the pyridine nucleotides and describe the overall pool, NAD^+ or $NADP^+$ the oxidised form, NADH or NADPH the reduced form.