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Urinary Water-Soluble Vitamins as Nutritional Biomarker to Estimate Their Intakes

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1. Introduction

The traditional approach of nutritional assessment is to survey the amount of nutrients consumed by dietary assessment. Although this method can provide approximate intake, this approach often makes misreporting, and can't determine nutritional status. Especially, to determine micronutrient intake by dietary assessment is difficult because of high variations in habitual micronutrient intake. A nutritional biomarker can be an indicator of nutritional status with respect to intake or metabolism of dietary constituents. The nutritional biomarkers can be designated into one or more of three categories, 1) a means of validation of dietary instruments, 2) surrogate indicators of dietary intakes, or 3) integrated measures of nutritional status for a nutrient (Potischman & Freudenheim, 2003). Recent validation studies have developed the urinary compounds as nutritional biomarkers to estimate nutrient intakes. For example, 24-hr urinary nitrogen has been established as a biomarker for protein intake (Bingham, 2003), same as urinary potassium and potassium intake (Tasevska et al., 2006), and urinary sugars for sugar intake (Tasevska et al., 2005).

Water-soluble vitamins are absorbed from the digestive tract after ingestion, stored in the liver, delivered to peripheral, and then excreted to urine (Food and Nutrition Board, Institute of Medicine, 1998). Urinary water-soluble vitamins or their metabolites decrease markedly as vitamin status declines, and they are affected by recent dietary intake (Food and Nutrition Board, Institute of Medicine, 1998). Urinary excretion of water-soluble vitamins such as thiamin, riboflavin and niacin has been used for setting Dietary Reference Intakes (DRIs) in USA and Japan (Food and Nutrition Board, Institute of Medicine, 1998; The Ministry of Health, Labour, and Welfare, 2009). Although pharmacological dose of water-soluble vitamin intake such as vitamin B₂ (Zempleni et al., 1996), nicotinamide (Shibata & Matsuo, 1990) and biotin (Zempleni & Mock, 1999) dramatically increase urinary vitamin levels, a few study had studied about the relationship between several oral dose correspond to dietary intake and urinary excretion of vitamin C (Levine et al., 1996, 2001). Thus, little attention had been paid to assess the quantitative relationships between intakes and urinary excretion of water-soluble vitamins. However, only a single study had investigated urinary vitamin as a possible marker for intake until 2007. Individuals' 30-day means of thiamin intake are highly correlated with their mean 24-hr urine thiamin levels under strictly controlled condition, showing 24-hr urinary thiamin as a useful marker for thiamin intake under strictly controlled conditions (Tasevska et al., 2007).

In the present review, recent findings from our intervention and cross-sectional studies are described to contribute to the establishment and effective use of urinary water-soluble vitamins as potential nutritional biomarkers. Furthermore, we propose the reference values for urinary water-soluble vitamins to show adequate nutritional status based on the findings. Our findings suggest that urinary water-soluble vitamins can be used as nutritional biomarkers to assess their mean intakes in groups. More accurate estimation of individuals' water-soluble vitamin intakes based on urinary excretion requires additional, precise biological information such as the bioavailability, absorption rate, and turnover rate.

2. Intervention studies

2.1 Factors affecting the urinary excretion of water-soluble vitamins

Urinary excretion of water-soluble vitamins varied among subjects more than blood levels did (Shibata et al., 2009). One possible explanation is that one or more of several factors such as nutrient requirements, energy expenditure, tissue turnover, intestinal absorption, kidney reabsorption, and physical characteristics differ between individuals. In fact, urinary excretion of vitamin B₁ is varied with the urine volume (Ihara et al., 2008), and furosemide-induced diuresis increases vitamin B₁ excretion rate (Rieck et al., 1999). Physical characteristics also affect the amount of urinary compounds. For example, individuals excreting higher urinary nitrogen had greater weight and body mass index (BMI) than those excreting average or lower nitrogen (Bingham et al., 1995), and creatinine clearance is positively correlated with BMI (Gerchman, 2009). In this context, the physical characteristics and urine volume may affect urinary excretion of B-group vitamins. We measured urinary excretion of B-group vitamins in free-living, healthy human subjects, and determined the correlations between each of the urinary B-group vitamins and factors such as physical characteristics and urine volume (Fukuwatari, 2009).

Twenty four-hr urine samples were collected from 186 free-living Japanese females aged 19–21 years, and 104 free-living Japanese elderly aged 70–84 years, and correlations were determined between urinary output of each B-group vitamin and body height, body weight, body mass index, body surface area, urine volume, and urinary creatinine. Only urinary excretion of vitamin B₁₂ showed strong correlation with urine volume in both young female and elderly subjects ($r = 0.683$, $p < 0.001$ and $r = 0.523$, $p < 0.001$, respectively). All factors such as urine volume, urinary creatinine and physical characteristics such as body height, body weight, BMI and body surface area showed weak or no correlations with other 7 urinary B-group vitamins including thiamin, riboflavin, pyridoxal metabolite 4-pyridoxic acid, sum of nicotinamide metabolites, pantothenic acid, folate and biotin. To determine how urinary vitamin B₁₂ is affected by its intake and urine volume, healthy Japanese adults (10 men; mean age, 25.9 ± 1.0 years; 10 women; mean age, 23.5 ± 6.4 years) orally administrated 1.5 mg cyanocobalamin, which is 500-fold higher daily intake. The Twenty Japanese adults consumed similar foods for 3 days and took a 1.5-mg cyanocobalamin tablet after breakfast on day 2. The 24-hour urine sample was collected for 3 successive days, and Pearson correlation coefficients between urinary vitamin B₁₂ and urine volume on each day were determined.

Pharmacologic dose of cyanocobalamin increased Urinary vitamin B₁₂ only 1.3-fold, and its concentration was not affected (Fig. 1A). Urinary vitamin B₁₂ was always strongly correlated

with urine volume even on the day before, the day of, and the day after intake (Fig. 1B-D). These results clearly showed that urinary excretion of vitamin B₁₂ was dependent upon urine volume, but not on intake of vitamin B₁₂. Vitamin B₁₂ is different from other B-group vitamins with respect to main excretion route, which is through the bile, and <10% of the total loss of vitamin B₁₂ from the body is through urine (Shinton, 1972). These results suggest that the change in the level of urinary vitamin B₁₂ is too small to evaluate intake of vitamin B₁₂, and thus urinary vitamin B₁₂ was unavailable to be used as biomarker for estimation of its intake. To excrete vitamin B₁₂ into urine, vitamin B₁₂ binds to carrier protein transcobalamin (TC) in serum (Allen, 1975), the TC-vitamin B₁₂ complex is filtered in the glomeruli, and the proximal convoluted tubule reabsorbs this complex via a receptor-mediated system (Birn, 2006). Megalin is an essential receptor for reabsorption of the TC-vitamin B₁₂ complex in the proximal tubule (Birn et al., 2002), binds to the TC-vitamin B₁₂ complex with an estimated affinity (K_d) of ~183 nmol/L (Moestrup et al., 1996). This high affinity may explain why urinary loss of vitamin B₁₂ is very low. However, little is known about how water regulation mediated by regulatory factors such as aquaporin, vasopressin and angiotensin is linked to reabsorption of vitamin B₁₂.

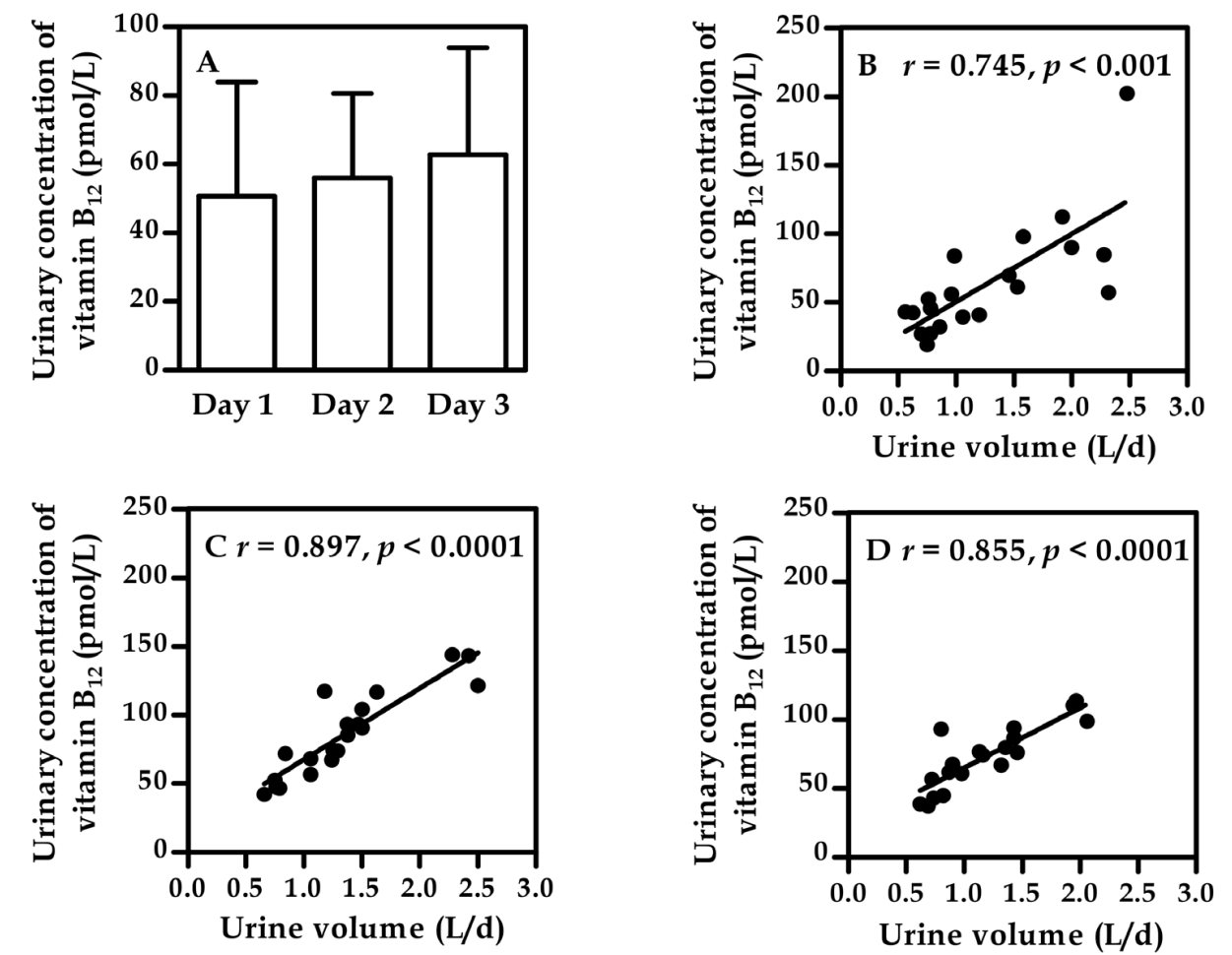


Fig. 1. Effect of administration of a pharmacologic dose of cyanocobalamin on urinary concentration of vitamin B₁₂ (A) and the correlations between urinary vitamin B₁₂ and urine volume on the day before cyanocobalamin intake (B), the day of intake (C) and the day after intake (D) (Fukuwatari et al., 2009).

2.2 Determination of urinary water-soluble vitamins as biomarkers for evaluating its intakes under strictly controlled conditions

As mentioned above, it is well known that pharmacological dose of water-soluble vitamin intake dramatically increase urinary vitamin levels, but a few study had studied about the relationship between several oral dose correspond to dietary intake and urinary excretion of vitamin C (Levine et al., 1996, 2001). We also determined whether urinary levels of water-soluble vitamins and their metabolites can be used as possible markers for estimating their intakes in the intervention study (Fukuwatari & Shibata, 2008). Six female Japanese college students participated to the intervention study, and their age, body weight, height and BMI (mean \pm SD) were 21.0 ± 0.0 years old, 161.7 ± 1.7 cm, 51.2 ± 2.8 kg and 19.6 ± 1.2 , respectively. They were given a standard Japanese diet in the first week, same diet with synthesized water-soluble vitamin mixture as the diet as approximately one-fold vitamin mixture based on DRIs for Japanese in the second week, with three-fold vitamin mixture in the third week, and six-fold mixture in the fourth week. The 24-hr urine was collected on each week, and the relationships were determined between oral dose and urinary vitamin levels. All urinary vitamin and their metabolites levels except vitamin B₁₂ increased linearly in a dose-dependent manner, and highly correlated with vitamin intake ($r = 0.959$ for vitamin B₁, $r = 0.927$ for vitamin B₂, $r = 0.965$ for vitamin B₆, $r = 0.957$ for niacin, $r = 0.934$ for pantothenic acid, $r = 0.907$ for folic acid, $r = 0.962$ for biotin, and $r = 0.952$ for vitamin C; Fig. 2). These findings show that water-soluble vitamin and their metabolite levels in 24-hr urine reflect the vitamin intakes under strictly controlled conditions.

Humans can synthesize the vitamin nicotinamide from tryptophan in the liver, and the resultant nicotinamide is distributed to non-hepatic tissues. The purpose of the synthetic pathway in the liver is not the supply of NAD⁺ but the supply of nicotinamide for non-hepatic tissues. The conversion pathway of nicotinamide from tryptophan is affected by various nutrients (Shibata et al., 1995, 1997a, 1998; Kimura et al., 2005), hormones (Shibata, 1995; Shibata & Toda, 1997), exercise (Fukuwatari et al., 2001) and drugs (Shibata et al., 1996, 1997b, 2001; Fukuwatari et al., 2004), based on data concerning the urinary excretion of metabolic intermediates in the tryptophan-nicotinamide pathway. However, the intervention study showed that administration of nicotinamide did not affect de novo nicotinamide synthesis from tryptophan (Fukuwatari & Shibata, 2007).

3. Cross-sectional studies: Determination of urinary water-soluble vitamins as biomarkers for evaluating its intakes in free-living subjects

The intervention study showed that urinary water-soluble vitamin levels are correlated highly with their intake in a strictly controlled environment (Fukuwatari & Shibata, 2008). Performance of a study under a free-living environment without any interventions is the next step to confirm the applicability of methods using a biomarker. Thus, we conducted the Values are individual points of six subjects in each dose. 4-PIC signifies 4-pyridoxic acid, a catabolite of pyridoxal, and the Nam metabolites signify the total amount of nicotinamide metabolites, N¹-methylnicotinamide (MNA), N¹-methyl-2-pyridone-5-carboxamide (2-Py) and N¹-methyl-4-pyridone-3-carboxamide (4-Py).

Cross-sectional studies, and free-living healthy subjects who were 216 university dietetics students aged 18-27 years, 114 Japanese elementary school children aged 10-12 years and 37

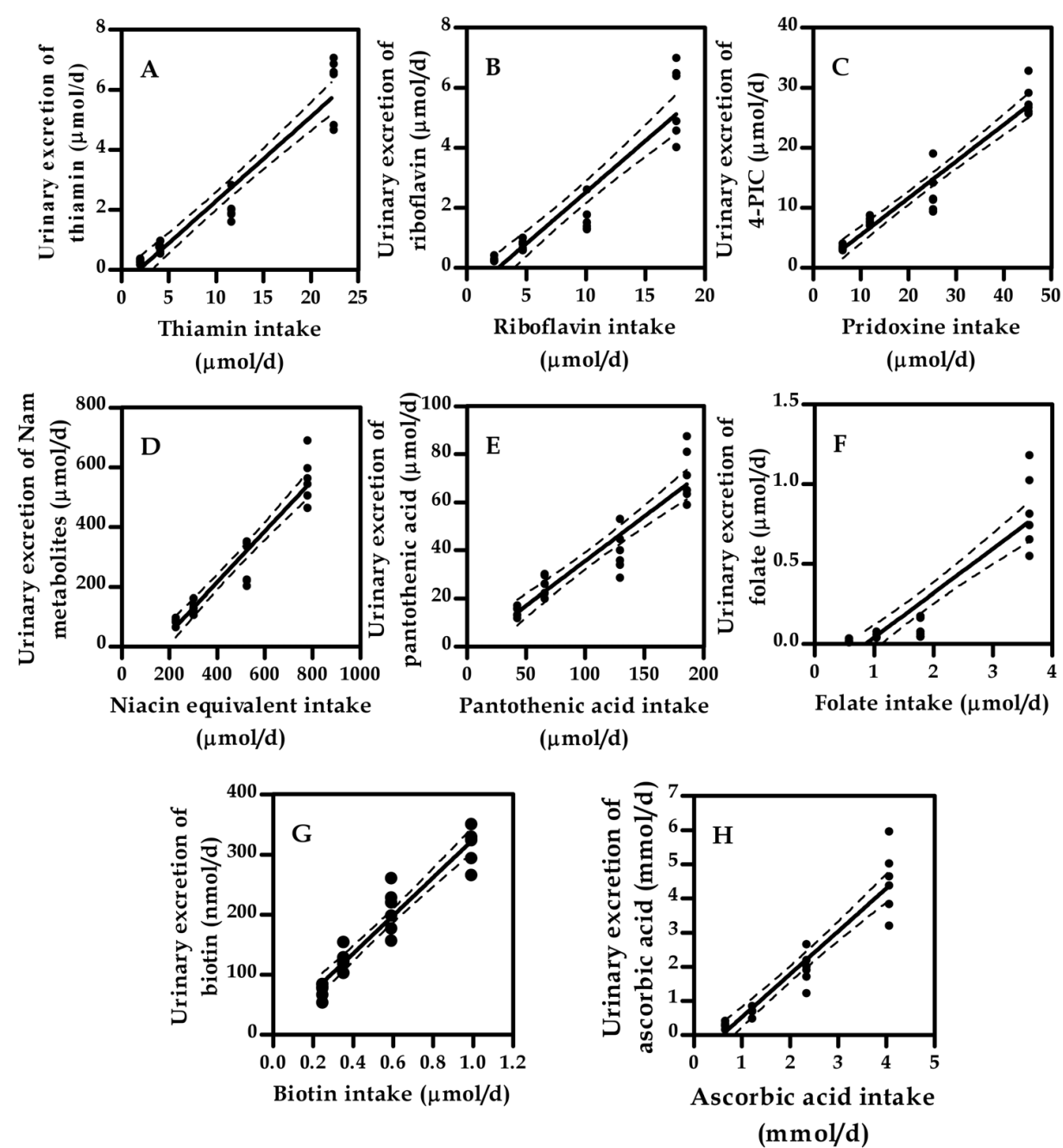


Fig. 2. Regression and 95% CI of oral dose and urinary excretion of vitamin B₁ (A), vitamin B₂ (B), vitamin B₆ (C), niacin (D), pantothenic acid (E), folate (F), biotin (G) and vitamin C (H) (Fukuwatari et al., 2008).

Japanese elderly females aged 70–84 years were participated (Tsuji et al., 2010a, 2010b, 2011). The subjects performed 4-day dietary assessment by recording all food consumed during the consecutive 4-day period with a weighed food record, and collected 24-hr urine samples on the fourth day. The results showed that the correlation between the urinary excretion and the dietary intake on the same day as urine collection was highest compared with the correlations on other days in each generation (Table 1-3). Moreover, the correlations between the urinary excretion and the mean dietary intakes during the recent 2–4 days

Vitamins	24-h urinary excretion of vitamin ^a	Vitamin intake at Day 4		Vitamin intake at Day 3		Vitamin intake at Day 2		Vitamin intake at Day 1	
	mean ± SD	mean ± SD	<i>r</i> ^b	mean ± SD	<i>r</i> ^b	mean ± SD	<i>r</i> ^b	mean ± SD	<i>r</i> ^b
Vitamin B ₁	0.425 ± 0.286 (μmol/d)	2.27 ± 0.92 (μmol/d)	0.29 [§]	2.46 ± 1.06 (μmol/d)	0.35 [§]	2.46 ± 1.00 (μmol/d)	0.27 [§]	2.09 ± 0.84 (μmol/d)	0.12
Vitamin B ₂	0.382 ± 0.321 (μmol/d)	3.32 ± 1.09 (μmol/d)	0.32 [§]	3.47 ± 1.35 (μmol/d)	0.28 [§]	3.43 ± 1.35 (μmol/d)	0.31 [§]	3.17 ± 1.46 (μmol/d)	0.11
Vitamin B ₆	3.68 ± 1.31 (μmol/d)	5.30 ± 2.15 (μmol/d)	0.26 [‡]	5.62 ± 2.38 (μmol/d)	0.37 [§]	5.83 ± 2.14 (μmol/d)	0.21 [‡]	5.25 ± 2.37 (μmol/d)	0.21 [‡]
Vitamin B ₁₂	0.028 ± 0.018 (nmol/d)	2.88 ± 3.42 (nmol/d)	0.05	3.59 ± 3.86 (nmol/d)	0.01	3.49 ± 5.16 (nmol/d)	-0.06	3.05 ± 5.69 (nmol/d)	0.10
Niacin	---	90.8 ± 39.4 (μmol/d)	0.32 [§]	96.5 ± 45.7 (μmol/d)	0.26 [‡]	98.8 ± 39.5 (μmol/d)	0.17 [*]	93.4 ± 49.0 (μmol/d)	0.22 [‡]
Niacin equivalent	84.5 ± 28.1 (μmol/d)	184 ± 65 (μmol/d)	0.29 [§]	191 ± 70 (μmol/d)	0.24 [‡]	196 ± 63 (μmol/d)	0.20 [*]	184 ± 74 (μmol/d)	0.21 [*]
Pantothenic acid	16.5 ± 5.2 (μmol/d)	23.6 ± 8.2 (μmol/d)	0.33 [§]	23.9 ± 8.5 (μmol/d)	0.44 [§]	24.3 ± 9.6 (μmol/d)	0.28 [§]	22.7 ± 11.2 (μmol/d)	0.10
Folate	23.1 ± 8.8 (nmol/d)	569 ± 338 (nmol/d)	0.15	591 ± 321 (nmol/d)	0.24 [‡]	610 ± 423 (nmol/d)	0.19 [*]	569 ± 515 (nmol/d)	0.07
Vitamin C	139 ± 131 (μmol/d)	425 ± 362 (μmol/d)	0.29 [§]	476 ± 354 (μmol/d)	0.34 [§]	546 ± 435 (μmol/d)	0.16	388 ± 276 (μmol/d)	0.22 [‡]

^aUrinary excretion for each vitamin corresponds to thiamin for vitamin B₁, riboflavin for vitamin B₂, 4-PIC for vitamin B₆, the sum of nicotinamide, MNA, 2-Py and 4-Py for niacin equivalent, the sum of reduced and oxidized ascorbic acid and 2,3-diketogluconic acid for vitamin C.

^b*r* means a correlation between urinary excretion and dietary intake of vitamin, for which values are denoted as **P*<0.05, ‡*P*<0.01, §*P*<0.001

Table 1. Measured values for 24-hr urinary excretion collected on Day 4 and daily vitamin intake for each water-soluble vitamin, and correlation between 24-hr urinary excretion and daily vitamin intake in young Japanese (n=148) (Tsuji et al., 2010a).

showed higher correlations, except for vitamin B₁₂, than those for daily intakes (Table 4-6). However, these correlations ranged from 0.27 to 0.59, and these modest correlations were not enough to use urinary vitamins as biomarkers to estimate their intakes in individuals. Several factors are known to affect water-soluble vitamin metabolism. For example, alcohol, carbohydrate and physical activity are expected to affect vitamin B₁ metabolism (Hoyumpa et al., 1977; Manore, 2000; Elmadfa et al., 2001); bioavailability of pantothenic acid in food is half that of free pantothenic acid (Tarr et al., 1981); and the single nucleotide polymorphism

of methylenetetrahydrofolate reductase (MTHFR) gene affects folate metabolism (Bagley & Selhub, 1998). When estimated intake of water-soluble vitamins was calculated using mean recovery rate and urinary excretion values, estimated water-soluble vitamin intakes except vitamin B₁₂ were correlated with 3-day mean intakes, and showed 91–107% of their 3-day mean intakes, except vitamin B₁₂ (61–79%) (Table 2). These findings showed that urinary water-soluble vitamins reflected their dietary intake over the past few days, and could be used as biomarkers to assess their intakes in groups.

Vitamins	24-h urinary excretion of vitamin ^a	Vitamin intake at Day 4		Vitamin intake at Day 3		Vitamin intake at Day 2		Vitamin intake at Day 1	
	mean ± SD	mean ± SD	<i>r</i> ^b	mean ± SD	<i>r</i> ^b	mean ± SD	<i>r</i> ^b	mean ± SD	<i>r</i> ^b
Vitamin B ₁	0.766 ± 0.383 (μmol/d)	3.13 ± 1.01 (μmol/d)	0.41 [§]	2.90 ± 0.85 (μmol/d)	0.25 [‡]	2.60 ± 0.74 (μmol/d)	0.22 [*]	2.75 ± 0.92 (μmol/d)	0.07
Vitamin B ₂	0.290 ± 0.209 (μmol/d)	3.47 ± 0.94 (μmol/d)	0.36 [§]	3.75 ± 1.13 (μmol/d)	0.36 [§]	3.59 ± 1.00 (μmol/d)	0.33 [§]	3.60 ± 1.17 (μmol/d)	0.23 [*]
Vitamin B ₆	2.36 ± 0.92 (μmol/d)	5.93 ± 1.86 (μmol/d)	0.42 [§]	5.96 ± 1.65 (μmol/d)	0.32 [§]	5.97 ± 1.69 (μmol/d)	0.36 [§]	6.00 ± 2.41 (μmol/d)	0.17
Vitamin B ₁₂	0.026 ± 0.015 (nmol/d)	3.15 ± 1.97 (nmol/d)	0.18	4.85 ± 5.93 (nmol/d)	0.14	4.76 ± 4.29 (nmol/d)	-0.02	4.64 ± 3.37 (nmol/d)	0.11
Niacin	---	97.0 ± 32.3 (μmol/d)	0.28 [§]	101.7 ± 38.2 (μmol/d)	0.11	105.3 ± 31.3 (μmol/d)	0.21 [*]	101.4 ± 32.5 (μmol/d)	0.23 [*]
Niacin equivalent	65.6 ± 27.6 (μmol/d)	214 ± 56 (μmol/d)	0.28 [‡]	218 ± 56 (μmol/d)	0.23 [‡]	218 ± 52 (μmol/d)	0.16	218 ± 56 (μmol/d)	0.25 [‡]
Pantothenic acid	11.6 ± 5.5 (μmol/d)	27.6 ± 6.9 (μmol/d)	0.23 [*]	30.1 ± 7.4 (μmol/d)	0.20 [*]	27.0 ± 6.3 (μmol/d)	0.31 [§]	28.7 ± 7.8 (μmol/d)	0.25 [‡]
Folate	16.8 ± 6.6 (nmol/d)	575 ± 170 (nmol/d)	0.27 [‡]	615 ± 423 (nmol/d)	0.12	491 ± 123 (nmol/d)	0.18	532 ± 164 (nmol/d)	0.24 [*]
Vitamin C	161 ± 221 (μmol/d)	477 ± 225 (μmol/d)	0.35 [§]	448 ± 313 (μmol/d)	0.23 [*]	403 ± 289 (μmol/d)	0.26 [‡]	445 ± 328 (μmol/d)	0.18

^aUrinary excretion for each vitamin corresponds to thiamin for vitamin B₁, riboflavin for vitamin B₂, 4-PIC for vitamin B₆, the sum of nicotinamide, MNA, 2-Py and 4-Py for niacin equivalent, the sum of reduced and oxidized ascorbic acid and 2,3-diketogluconic acid for vitamin C.

^b*r* means a correlation between urinary excretion and dietary intake of vitamin, for which values are denoted as ^{*}*P*<0.05, [‡]*P*<0.01, [§]*P*<0.001

Table 2. Measured values for 24-hr urinary excretion collected on Day 4 and daily vitamin intake for each water-soluble vitamin, and correlation between 24-hr urinary excretion and daily vitamin intake in Japanese school children (n=114) (Tsuji et al., 2010b).

Vitamins	24-h urinary excretion of vitamin ^a	Vitamin intake at Day 4		Vitamin intake at Day 3		Vitamin intake at Day 2		Vitamin intake at Day 1	
	mean ± SD	mean ± SD	<i>r</i> ^b	mean ± SD	<i>r</i> ^b	mean ± SD	<i>r</i> ^b	mean ± SD	<i>r</i> ^b
Vitamin B ₁	0.459 ± 0.494 (μmol/d)	2.51 ± 0.91 (μmol/d)	0.47 [‡]	2.50 ± 0.73 (μmol/d)	0.54 [§]	2.62 ± 0.85 (μmol/d)	0.28	2.37 ± 0.74 (μmol/d)	0.42 [*]
Vitamin B ₂	0.852 ± 0.828 (μmol/d)	3.47 ± 1.22 (μmol/d)	0.49 [‡]	3.60 ± 1.08 (μmol/d)	0.46 [‡]	3.69 ± 1.12 (μmol/d)	0.52 [§]	3.54 ± 1.14 (μmol/d)	0.34 [*]
Vitamin B ₆	4.45 ± 2.26 (μmol/d)	7.06 ± 2.78 (μmol/d)	0.37 [*]	7.04 ± 2.35 (μmol/d)	0.13	7.57 ± 2.71 (μmol/d)	0.34 [*]	7.45 ± 2.41 (μmol/d)	0.16
Vitamin B ₁₂	0.034 ± 0.035 (nmol/d)	5.81 ± 4.91 (nmol/d)	0.15	5.89 ± 5.31 (nmol/d)	-0.07	4.95 ± 4.31 (nmol/d)	0.12	6.75 ± 8.43 (nmol/d)	-0.03
Niacin	---	113 ± 49 (μmol/d)	0.35 [*]	127 ± 57 (μmol/d)	0.38 [*]	129 ± 65 (μmol/d)	0.39 [*]	121 ± 47 (μmol/d)	0.32
Niacin equivalent	89.7 ± 30.8 (μmol/d)	213 ± 72 (μmol/d)	0.37 [*]	232 ± 73 (μmol/d)	0.45 [‡]	239 ± 94 (μmol/d)	0.39 [*]	223 ± 71 (μmol/d)	0.26
Pantothenic acid	15.1 ± 6.2 (μmol/d)	26.1 ± 8.9 (μmol/d)	0.59 [§]	25.5 ± 8.9 (μmol/d)	0.49 [‡]	25.6 ± 6.4 (μmol/d)	0.46 [‡]	24.5 ± 7.1 (μmol/d)	0.30
Folate	36.6 ± 16.9 (nmol/d)	792 ± 305 (nmol/d)	0.55 [§]	845 ± 360 (nmol/d)	0.24	854 ± 301 (nmol/d)	0.48 [‡]	818 ± 366 (nmol/d)	0.28
Vitamin C	214 ± 271 (μmol/d)	627 ± 310 (μmol/d)	0.46 [‡]	620 ± 407 (μmol/d)	0.43 [‡]	722 ± 423 (μmol/d)	0.39 [*]	642 ± 356 (μmol/d)	0.53 [§]

^aUrinary excretion for each vitamin corresponds to thiamin for vitamin B₁, riboflavin for vitamin B₂, 4-PIC for vitamin B₆, the sum of nicotinamide, MNA, 2-Py and 4-Py for niacin equivalent, the sum of reduced and oxidized ascorbic acid and 2,3-diketogluconic acid for vitamin C.

^b*r* means a correlation between urinary excretion and dietary intake of vitamin, for which values are denoted as ^{*}*P*<0.05, [‡]*P*<0.01, [§]*P*<0.001

Table 3. Measured values for 24-hr urinary excretion collected on Day 4 and daily vitamin intake for each water-soluble vitamin, and correlation between 24-hr urinary excretion and daily vitamin intake in elderly Japanese (n=35) (Tsuji et al., 2011).

Vitamins	2 days mean vitamin intake (Days 3–4)		3 days mean vitamin intake (Days 2–4)		4 days mean vitamin intake (Days 1–4)		Recovery rate ^c (%)	Mean estimated vitamin intake ^d		
	mean ± SD	<i>r^a</i>	mean ± SD	<i>r^a</i>	mean ± SD	<i>r^a</i>		mean ± SD	<i>r^e</i>	% ratio ^f
Vitamin B ₁	2.37 ± 0.79 (μmol/d)	0.40 [§]	2.40 ± 0.73 (μmol/d)	0.42 [§]	2.32 ± 0.63 (μmol/d)	0.39 [§]	17.8 ± 11.4	2.38 ± 1.61 (μmol/d)	0.40 [§]	100%
Vitamin B ₂	3.04 ± 0.87 (μmol/d)	0.39 [§]	3.05 ± 0.83 (μmol/d)	0.43 [§]	3.00 ± 0.81 (μmol/d)	0.39 [§]	12.4 ± 10.0	3.08 ± 2.59 (μmol/d)	0.38 [§]	101%
Vitamin B ₆	5.46 ± 1.85 (μmol/d)	0.40 [§]	5.58 ± 1.62 (μmol/d)	0.40 [§]	5.50 ± 1.54 (μmol/d)	0.39 [§]	69.6 ± 28.6	5.29 ± 1.88 (μmol/d)	0.40 [§]	95%
Vitamin B ₁₂	3.24 ± 2.62 (nmol/d)	0.06	3.32 ± 2.60 (nmol/d)	0.02	3.23 ± 2.84 (nmol/d)	0.07	1.4 ± 1.5	2.04 ± 1.33 (nmol/d)	0.06	61%
Niacin	93.6 ± 33.7 (μmol/d)	0.35 [§]	95.4 ± 28.7 (μmol/d)	0.33 [§]	94.9 ± 28.7 (μmol/d)	0.33 [§]	---	---	---	---
Niacin equivalent	189 ± 54 (μmol/d)	0.33 [§]	192 ± 47 (μmol/d)	0.32 [§]	190 ± 47 (μmol/d)	0.32 [§]	45.8 ± 16.0	184 ± 61 (μmol/d)	0.33 [§]	96%
Pantothenic acid	23.7 ± 7.0 (μmol/d)	0.47 [§]	23.9 ± 6.7 (μmol/d)	0.46 [§]	23.6 ± 7.0 (μmol/d)	0.41 [§]	71.6 ± 23.3	23.0 ± 7.3 (μmol/d)	0.47 [§]	96%
Folate	583 ± 243 (nmol/d)	0.24 [‡]	593 ± 243 (nmol/d)	0.27 [‡]	588 ± 273 (nmol/d)	0.24 [‡]	4.3 ± 1.9	540 ± 206 (nmol/d)	0.24 [‡]	91%
Vitamin C	446 ± 285 (μmol/d)	0.44 [§]	478 ± 267 (μmol/d)	0.42 [§]	455 ± 244 (μmol/d)	0.41 [§]	31.3 ± 29.6	446 ± 420 (μmol/d)	0.44 [§]	93%

^aMean dietary intake was calculated using daily dietary intake for each individual.
^b*r* means a correlation between 24-h urinary excretion and mean dietary intake.
^cRecovery rate was derived from 24-h urinary excretion/3-Days mean intake.
^dMean estimated intake was calculated using 24-hr urinary excretion and recovery rate.
^e*r* means a correlation between 3-day mean dietary intake and mean estimated intake.
^f% ratio means a ratio between 3-day mean intake and mean estimated intake.
**P*<0.05, [‡]*P*<0.01, [§]*P*<0.001.

Table 4. Correlations between 24-hr urinary excretion and mean vitamin intakes, recovery rates, and mean estimated intakes in young Japanese (n=148) (Tsuji et al., 2010a).

Vitamins	2 days mean vitamin intake (Days 3–4)		3 days mean vitamin intake (Days 2–4)		4 days mean vitamin intake (Days 1–4)		Recovery rate ^c (%)	Mean estimated vitamin intake ^d		
	mean ± SD	<i>r</i> ^a	mean ± SD	<i>r</i> ^a	mean ± SD	<i>r</i> ^a		mean ± SD	<i>r</i> ^e	% ratio ^f
Vitamin B ₁	3.02 ± 0.77 (μmol/d)	0.42§	2.88 ± 0.63 (μmol/d)	0.42§	2.85 ± 0.58 (μmol/d)	0.35§	27.6 ± 12.2	2.83 ± 1.42 (μmol/d)	0.37§	10 0%
Vitamin B ₂	3.61 ± 0.85 (μmol/d)	0.41§	3.60 ± 0.79 (μmol/d)	0.43§	3.60 ± 0.78 (μmol/d)	0.42§	7.9 ± 5.2	3.66 ± 2.63 (μmol/d)	0.26‡	10 2%
Vitamin B ₆	5.94 ± 1.41 (μmol/d)	0.45§	5.95 ± 1.29 (μmol/d)	0.49§	5.96 ± 1.35 (μmol/d)	0.43§	39.8 ± 14.0	5.90 ± 2.30 (μmol/d)	0.41§	10 0%
Vitamin B ₁₂	4.00 ± 3.14 (nmol/d)	0.19*	4.25 ± 2.55 (nmol/d)	0.10	4.35 ± 2.10 (nmol/d)	0.10	0.7 ± 0.6	3.72 ± 2.14 (nmol/d)	0.06	79 %
Niacin	99 ± 26 (μmol/d)	0.24*	101 ± 21.7 (μmol/d)	0.29‡	101 ± 20.4 (μmol/d)	0.32§	---	---	---	---
Niacin equivalent	216 ± 48 (μmol/d)	0.29‡	217 ± 43 (μmol/d)	0.29‡	217 ± 39 (μmol/d)	0.32§	30.7 ± 12.6	215 ± 91 (μmol/d)	0.20*	99 %
Pantothenic acid	28.8 ± 6.0 (μmol/d)	0.26‡	28.2 ± 5.6 (μmol/d)	0.32§	28.3 ± 5.7 (μmol/d)	0.32§	41.4 ± 19.5	28.1 ± 13.3 (μmol/d)	0.27‡	99 %
Folate	595 ± 236 (nmol/d)	0.23*	560 ± 174 (nmol/d)	0.24*	553 ± 147 (nmol/d)	0.27‡	3.1 ± 1.3	536 ± 211 (nmol/d)	0.09	97 %
Vitamin C	462 ± 200 (μmol/d)	0.39§	442 ± 183 (μmol/d)	0.39§	443 ± 170 (μmol/d)	0.39§	36.4 ± 50.3	447 ± 613 (μmol/d)	0.39§	10 0%

^aMean dietary intake was calculated using daily dietary intake for each individual
^b*r* means a correlation between 24-h urinary excretion and mean dietary intake.
^cRecovery rate was derived from 24-h urinary excretion/3-Days mean intake.
^dMean estimated intake was calculated using 24-hr urinary excretion and recovery rate.
^e*r* means a correlation between 3-day mean dietary intake and mean estimated intake
^f% ratio means a ratio between 3-day mean intake and mean estimated intake.
**P*<0.05, ‡*P*<0.01, §*P*<0.001.

Table 5. Correlations between 24-hr urinary excretion and mean vitamin intakes, recovery rates, and mean estimated intakes in Japanese school children (n=114) (Tsuji et al., 2010b).

Vitamins	2 days mean vitamin intake (Days 3–4)		3 days mean vitamin intake (Days 2–4)		4 days mean vitamin intake (Days 1–4)		Recovery rate ^c (%)	Mean estimated vitamin intake ^d		
	mean ± SD	<i>r^a</i>	mean ± SD	<i>r^a</i>	mean ± SD	<i>r^a</i>		mean ± SD	mean ± SD	<i>r^e</i> % ratio ^f
Vitamin B ₁	2.51 ± 0.66 (μmol/d)	0.62 ^s	2.55 ± 0.62 (μmol/d)	0.58 ^s	2.50 ± 0.59 (μmol/d)	0.59 ^s	16.9 ± 17.7	2.71 ± 2.92 (μmol/d)	0.58 ^s	107 %
Vitamin B ₂	3.53 ± 1.03 (μmol/d)	0.53 ^s	3.59 ± 0.99 (μmol/d)	0.57 ^s	3.57 ± 0.95 (μmol/d)	0.55 ^s	23.1 ± 22.9	3.69 ± 3.58 (μmol/d)	0.52 ^s	103 %
Vitamin B ₆	7.05 ± 2.17 (μmol/d)	0.30	7.22 ± 2.01 (μmol/d)	0.35 [*]	7.58 ± 1.95 (μmol/d)	0.33	64.2 ± 31.7	6.93 ± 3.5 (μmol/d) ²	0.35 [*]	96 %
Vitamin B ₁₂	5.85 ± 3.55 (nmol/d)	-0.01	5.55 ± 3.16 (nmol/d)	0.01	5.85 ± 3.16 (nmol/d)	-0.03	0.9 ± 1.6	3.62 ± 3.73 (nmol/d)	0.12	65 %
Niacin	120 ± 42 (μmol/d)	0.46 [†]	123 ± 37 (μmol/d)	0.54 ^s	122 ± 36 (μmol/d)	0.52 ^s	---	---	---	---
Niacin equivalent	222 ± 58 (μmol/d)	0.50 [†]	228 ± 56 (μmol/d)	0.54 ^s	227 ± 55 (μmol/d)	0.49 [†]	40.1 ± 12.3	224 ± 77 (μmol/d)	0.54 ^s	98 %
Pantothenic acid	25.8 ± 8.1 (μmol/d)	0.58 ^s	25.8 ± 7.1 (μmol/d)	0.57 ^s	25.4 ± 6.5 (μmol/d)	0.56 ^s	59.6 ± 24.2	25.3 ± 10.4 (μmol/d)	0.46 [†]	98 %
Folate	819 ± 279 (nmol/d)	0.42 [*]	831 ± 257 (nmol/d)	0.47 [†]	828 ± 266 (nmol/d)	0.43 [†]	4.5 ± 2.0	805 ± 372 (nmol/d)	0.48 [†]	97 %
Vitamin C	624 ± 337 (μmol/d)	0.50 [†]	657 ± 339 (μmol/d)	0.50 [†]	653 ± 334 (μmol/d)	0.53 ^s	32.0 ± 39.3	682 ± 847 (μmol/d)	0.51 [†]	101 %

^aMean dietary intake was calculated using daily dietary intake for each individual.
^b*r* means a correlation between 24-h urinary excretion and mean dietary intake.
^cRecovery rate was derived from 24-h urinary excretion/3-Days mean intake.
^dMean estimated intake was calculated using 24-hr urinary excretion and recovery rate.
^e*r* means a correlation between 3-day mean dietary intake and mean estimated intake.
^f% ratio means a ratio between 3-day mean intake and mean estimated intake.
^{*}*P*<0.05, [†]*P*<0.01, ^s*P*<0.001.

Table 6. Correlations between 24-hr urinary excretion and mean vitamin intakes, recovery rates, and mean estimated intakes in elderly Japanese (n=35) (Tsuji et al., 2011).

Relatively low correlations were found between urinary folate and dietary intake in the cross-sectional studies, whereas a high correlation was found in the intervention study (Fukuwatari & Shibata, 2008). The relatively low correlation of folate in free-living subjects may be explained by several reasons. Urinary folate excretion responds slowly to change in dietary folate intake, and is reduced significantly in people who consume a low-folate diet (Kim & Lim, 2008). Some Japanese subjects consumed Japanese green tea and liver well, and these foods contain 16 μg/100 g and 1000 μg/100 g folate, respectively, in the Japanese Food Composition Table (The Ministry of Education, Culture, Sports, Science and Technology, 2007). The composition of Japanese tea may vary depending on whether the extract of tea was made personally or whether it was a bottled tea beverage, because the present Japanese Food Composition Table cannot differentiate such products. Similarly, since the Food

Composition Table only describes the composition of raw liver, an error exists between the quantity of vitamin intake obtained from the Food Composition Table and the actual intake from cooked liver. Nutrient intakes were calculated using this Food Composition Table which did not take account of cooking loss for the above foods, and thus this might cause potential low level of accuracy. There might be also a technical issue. Urinary intact folates were measured by a microbiological assay in the cross-sectional studies. However, folates are catabolized into *p*-aminobenzoylglutamate and the acetylated form, *p*-acetamidobenzoylglutamate, which are excreted into the urine (Wolfe et al., 2003).

4. Reference values for urinary water-soluble vitamins

Urinary water-soluble vitamins can be used as potential biomarker not only for estimation of its intake but also evaluation for its nutritional status. The intervention study comprehensively investigated urinary water-soluble vitamin values in subjects consuming semi-purified diet with vitamin mixture for 7 days (Shibata et al., 2005). The study revealed the mean values and ranges for each water-soluble vitamin except vitamin B₁₂ in the subjects with vitamin mixture based on DRIs for Japanese. Based on these results, we propose the reference values for urinary water-soluble vitamins to show adequate nutritional status in Table 7. When urinary excretion of some vitamins is lower than the lower reference value, subject may not intake its vitamin enough for DRIs. When urinary vitamin is higher than the upper value, subject may intake its vitamin supplement. These reference values may be useful for first screening to check one’s vitamin nutritional status and vitamin supplement intake.

Vitamins ^a	Reference values
Vitamin B ₁	300-2400 (nmol/d)
Vitamin B ₂	200-1800 (nmol/d)
Vitamin B ₆	3.0-16.0 (μmol/d)
Vitamin B ₁₂	---
Niacin	50-300 (μmol/d)
Pantothenic acid	10-60 (μmol/d)
Folate	15-80 (nmol/d)
Biotin	50-300 (nmol/d)
Vitamin C	150-2400 (μmol/d)

^aUrinary excretion for each vitamin corresponds to thiamin for vitamin B₁, riboflavin for vitamin B₂, 4-PIC for vitamin B₆, the sum of nicotinamide, MNA, 2-Py and 4-Py for niacin equivalent, the sum of reduced and oxidized ascorbic acid and 2,3-diketogluconic acid for vitamin C.

Table 7. Proposed reference values for urinary water-soluble vitamins in adults.

5. Conclusion

Recent studies have induced great advances for urinary water-soluble vitamins as biomarkers for its intakes. Measuring urinary water-soluble vitamin levels can be the good approach for assessing dietary vitamin intake in groups, and for simply evaluation of its nutritional status in individuals. However, there is limitation for its use; urinary vitamins have not been suitable biomarker to estimate its intake in individuals yet. More accurate

estimation of the dietary intake of water-soluble vitamins based on urinary excretion requires additional, precise biological information such as the bioavailability, absorption rate, and turnover rate. Next step in this type of study will be to determine whether vitamin contents in spot urine sample is used to assess water-soluble vitamin intakes in groups.

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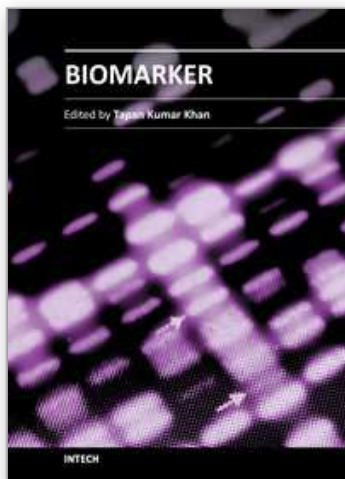
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