Asian Journal of Clinical Nutrition

ISSN 1992-1470

science alert

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OPEN ACCESS Asian Journal of Clinical Nutrition

ISSN 1992-1470
DOI: 10.3923/ajcn.2022.9.13

Commentary
Excessive Carbohydrate Intake is Misleadingly Considered to Increase Thiamine Requirement for Carbohydrate Metabolism

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Abstract

Thiamine (vitamin B_1) is a water-soluble and essential vitamin and act as a coenzyme after converting to thiamine pyrophosphate in crucial metabolic enzymes of pyruvate dehydrogenase, α-ketoglutarate dehydrogenase and transketolase. The original paper that investigated the influence of stepwise increases in carbohydrate intake on thiamine requirement seems to mislead the reader into considering an increase in thiamine requirement for excessive carbohydrate intake. Thiamine is reabsorbed in the brush border membrane of renal proximal tubular cells through thiamine transporters. The transport of thiamine with a stoichiometric thiamin/H^+ exchange of 1:1 is facilitated by the outward H^+ gradient and the low thiamine intracellular concentration maintained by its rapid conversion to thiamine pyrophosphate. The thiamine reabsorption is affected by the activity of Na^+/H^+ exchanger 3 secreting H^+ for the acidification of tubular fluid. The exit of thiamine into an interstitial fluid is coupled directly to the hydrolysis of ATP in sodium pump. The activity of Na^+/H^+ exchanger 3 has been demonstrated to be enhanced in diabetic patients and suppressed by sodium-glucose co-transporter 2 inhibitors. Excessive glucose reabsorption is presumed to inhibit the thiamin reabsorption in the proximal tubule, leading to an increase in urinary thiamine excretion as demonstrated in diabetic patients. Thiamine supplementation would not be required only for a carbohydrate-rich diet while keeping in mind the thiamine bioavailability and metabolism in the body. Further studies are needed to clarify the relationship between excessive carbohydrate intake and thiamine requirement.

Key words: Thiamine, vitamin B_1, thiamine requirement, thiamine transporter, urinary thiamine excretion, carbohydrate intake, glucose metabolism

Citation: Nago, Y., T. Mizuhashi and Y. Aoki, 2022. Excessive carbohydrate intake is misleadingly considered to increase thiamine requirement for carbohydrate metabolism. Asian J. Clin. Nutr., 14: 9-13.

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Thiamine (vitamin B_1) is a water-soluble and essential vitamin and acts as a coenzyme (prosthetic group) after converting to thiamine pyrophosphate in crucial metabolic enzymes of pyruvate dehydrogenase, α-ketoglutarate dehydrogenase and transketolase. Accordingly, reduced enzymatic activity in thiamine deficiency can result in altered mitochondrial activity, impaired oxidative metabolism and reduced energy production. Such alterations can affect many cells, especially neurons requiring high energy, leading to cell death. Wernicke's encephalopathy and congestive heart failure (dry beriberi and wet beriberi) are well-known complications in thiamine deficiency[1-3]. The thiamine deficiency is commonly caused by its inadequate intake and/or increased requirement. In this point, excessive carbohydrate intake is considered to increase the thiamine requirement for carbohydrate metabolism[1,3], presumably from misinterpretation. Theoretically, only an increase in the number of substrates, at least in a short duration, should not increase the requirement of thiamine as a coenzyme. The European Food Safety Authority Panel notes that there are limited data on the relationship between thiamine requirement and carbohydrate intake[2]. However, there seem to be quite a few healthcare professionals who even imagine as if thiamine would be consumed by carbohydrate metabolism.

Possible misinterpretation of thiamine requirement: The original paper[4], which investigated the influence of stepwise increases in dietary carbohydrate intake on thiamine requirement, has often been cited to support the idea that excessive carbohydrate intake increases the thiamine requirement for carbohydrate metabolism. The authors noted that increases in carbohydrate intake from 55-65% and 75% of total energy caused a significant ($p<0.05$) decrease in plasma and urine concentrations of thiamine as shown in Fig. 1. There were four-time points (T_0-T_3) in the three intervention periods (4 days each): the beginning (T_0) and end (T_1) of 55% carbohydrate period (55% C), the end (T_2) of 65% carbohydrate period (65% C) and the end (T_3) of 75% carbohydrate period (75% C). Erythrocyte transketolase activity, a functional test of thiamine status[2], remained unchanged during the three periods, where daily thiamine intake and total energy intake were kept constant. Accordingly, it may be natural to consider that excessive carbohydrate intake is meant to increase thiamine requirement or thiamine consumption. However, it was noticed that the statistical interpretation of the plasma and urine data was not correct. Although it was described that the Freedman test was performed to test for differences among the three-time points of T_1, T_2 and T_3 in the statistical analysis section, data including the time point of T_0 appeared to be included for the Freedman test, besides, with post hoc analysis. The urinary thiamine level decreased from T_1-T_3 after the adaptation period of 55% C as the authors noted but the level at T_3 was higher than that at T_2 while the plasma thiamine level also stopped decreasing. They insisted that the data suggested that urinary thiamine excretion decreased after stepwise increases in carbohydrate intake as a whole. However, another interpretation is possible that urinary thiamine excretion decreased from T_0-T_2 as if it had been the adaptation period and then increased from T_2-T_3 due to an effect of the increase of carbohydrate intake.

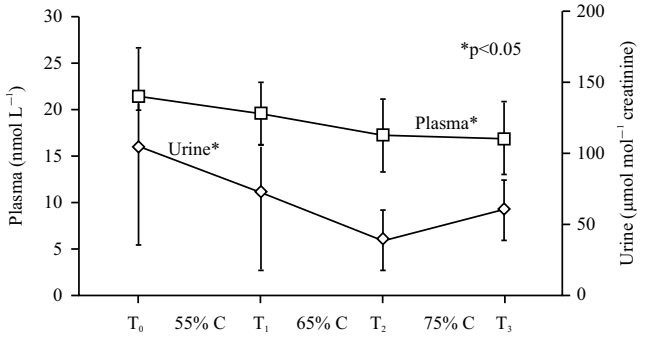

Fig. 1: Changes in plasma and urine concentrations of thiamine during the periods of stepwise increases in dietary carbohydrate intake reported by Elmadfa *et al.*[4] They noted that increases in carbohydrate intake from 55% to 65% and 75% of total energy caused a significant ($p<0.05$) decrease in plasma and urine concentrations of thiamine. Four-time points in the three intervention periods (4 days each): the beginning (T_0) and end (T_1) of 55% carbohydrate period (55% C), the end (T_2) of 65% carbohydrate period (65% C) and the end (T_3) of 75% carbohydrate period (75% C)

As a similar case of possible misinterpretation, a case report[5] demonstrated that glucose loading precipitated thiamine deficiency in malnourished patients with latent thiamine deficiency. Such clinical manifestations may also mislead the reader into considering an increase in the thiamine requirement for excessive carbohydrate intake. In thiamine deficiency, pyruvate dehydrogenase, a key enzyme that allows energy production in the citric acid cycle, cannot convert pyruvate to acetyl CoA. Instead, pyruvate is converted to lactate, possibly causing lactic acidosis[6]. Another case report[7] described rapid reversal of severe lactic acidosis after thiamine administration in hospitalized adult patients who had received parenteral nutrition without thiamine supplementation. A literature review[8] suggests that a delay in

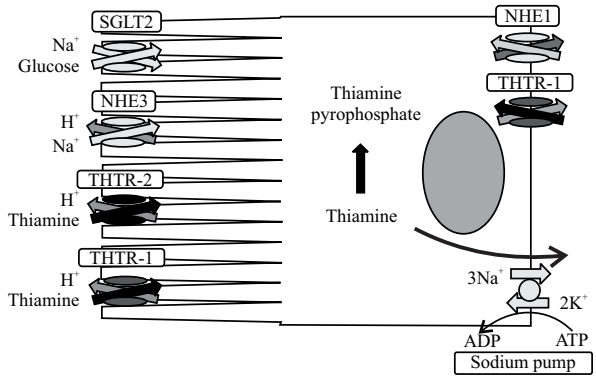

Fig. 2: An illustration of putative renal handling of thiamine in the proximal renal tubular cell

Thiamine is reabsorbed in the brush border membrane through thiamine transporter (THTR)-1 and THTR-2. The transport of thiamine with a stoichiometric thiamin/H^+ exchange of 1:1 is facilitated by the outward H^+ gradient and the low thiamine intracellular concentration maintained by its rapid conversion to thiamine pyrophosphate. The thiamine reabsorption is affected by the activity of the Na^+/H^+ exchanger (NHE) 3 secreting H^+ for the acidification of tubular fluid. The exit of thiamine into an interstitial fluid is coupled directly to the hydrolysis of ATP in sodium pump (Na^+/K^+-ATPase). The NHE3 activity is stimulated by physiological concentrations of glucose and suppressed by sodium-glucose co-transporter (SGLT) 2 inhibitors in stationary microperfusion experiments in rats[19]. It is presumed that excessive glucose reabsorption could lead to inhibiting the thiamin reabsorption in the proximal tubule

giving glucose to hypoglycemic patients with latent thiamine deficiency cannot be recommended, keeping in mind that prolong glucose supplementation without the addition of thiamine can be a risk factor for the development of Wernicke's encephalopathy. In thiamine-deficient rats, it was demonstrated that glucose loading caused focal lactic acidosis in the vulnerable medial thalamus, contributing to the pathogenesis of thalamic neuronal damage in Wernicke's encephalopathy[9].

Putative renal handling of thiamine: Based on the relevant reports[10-12], putative renal handling of thiamine in the proximal renal tubular cell is illustrated in Fig. 2. Thiamine is reabsorbed in the brush border membrane through thiamine transporter (THTR)-1 functioning at the micromolar range and THTR-2 functioning at the nanomolar range. The transport of thiamine with a stoichiometric thiamin/H^+ exchange of 1:1 is facilitated by the outward H^+ gradient and the low thiamine intracellular concentration maintained by its rapid conversion to thiamine pyrophosphate. The thiamine reabsorption is affected by the activity of the Na^+/H^+ exchanger (NHE) 3, which is responsible for the acidification of tubular fluid by secreting H^+ into the renal proximal tubule. The driving force for the NHE3 is the inward sodium gradient maintained by the sodium pump (Na^+/K^+-ATPase). The active exit of thiamine through the basolateral membrane of the tubular cells into an interstitial fluid is coupled directly to the hydrolysis of ATP involved in the sodium pump. Sodium-glucose co-transporter (SGLT) 2 driven by the inward sodium gradient in the brush border membrane[13] and NHE1 localized in the basolateral membrane[14] are also illustrated.

In the previous report[13], we presumed that the reabsorption of vitamin C at the renal proximal tubule through sodium-vitamin C co-transporter 1 driven by the inward sodium gradient could be increased by inhibiting the reabsorption of glucose through SGLT2 with the treatment of SGLT2 inhibitors. About thiamine, it has been demonstrated that compared with healthy people, patients with type 1 and type 2 diabetes had low plasma thiamine levels in association with increased renal clearance and fractional excretion of thiamine, without a decrease in erythrocyte transketolase activity[15]. When considering the reabsorption of thiamine at the renal proximal tubule to the glucose reabsorption, it needs to be considered that NHE3 lies between SGLT2 and THTR-2. The activity of NHE3 consisting of 12 transmembrane domains followed by a hydrophilic C terminus towards the cytoplasm is driven by the inward sodium gradient and regulated by some factors including protein kinases[14,16]. Since THTR-2, consisting of 12 transmembrane domains[17], is driven by the outward H^+ gradient[10], it is conceivable that the reabsorption of thiamine could be inhibited by a decrease in the outward H^+ gradient resulting from an increase in the activity of NHE3. The activity of NHE3 has been demonstrated to be increased in diabetic patients and decreased by SGLT2 inhibitors[18]. It was demonstrated that the NHE3 activity was stimulated by physiological concentrations of glucose and suppressed by SGLT2 inhibitors in stationary microperfusion experiments in rats[19]. Taken together, it is inferred that excessive carbohydrate intake could lead to an increase in urinary thiamine excretion, which needs to be clarified in further studies. As another mechanism, it was reported that high glucose concentrations induced down regulation of thiamine transporters in human primary proximal tubular cells[20].

Recommended daily intake of thiamine: The storage of thiamine in the human body is minimal but subjective symptoms of thiamine deficiency in adults appear after 2-3 weeks of a thiamine-deficient diet[21]. Excessive carbohydrate intake in people without diabetes would not readily cause thiamine deficiency without the persistent inadequate intake of thiamine, considering erythrocyte

transketolase activity maintained despite a large amount of urinary thiamine excretion in people with diabetes[15]. Understandably, continued high physical activity and energy metabolism would increase the requirement for thiamine due to an increase in mitochondrial enzymes and tissue turnover or repair[22]. It has been demonstrated that the median protein half-life of mouse intestinal epithelial cells was 3.5-4.2 days and that metabolic enzymes belonging to the glycolysis and citric acid cycle had the fastest turnover rates[23]. Human gastrointestinal epithelial turnover has been demonstrated to be about 2-5 days[24]. Less than one-third of the recommended daily requirements of vitamins including thiamine can cause problems in the exercise performance within 4 weeks[25]. The recommended daily intake of thiamine is 1.2 mg/day for men and 1.1 mg/day for women over age eighteen[3] or the population reference intake is 0.4 mg/1,000 kcal for all adults[2]. Collectively, thiamine supplementation would not be needed, at least, only for excessive carbohydrate intake, while considering inadequate intake of thiamine due to anti-thiamine factors such as heat-labile thiaminase and heat-stable thiamine antagonists (polyphenols and flavonoids) in foods[21].

CONCLUSION

Some reports on glucose metabolism and thiamine requirement seem to mislead the reader into considering an increase in thiamine requirement for excessive carbohydrate intake. From the relevant literature, it is inferred that excessive carbohydrate intake or carbohydrate-rich food intake in people without hyperglycemia could lead to a small increase, if any, in urinary thiamine excretion but not to an increase in thiamine requirement for glucose metabolism. Thiamine supplementation would not be required only for a carbohydrate-rich diet, although further studies are needed to clarify the relationship between excessive carbohydrate intake and thiamine requirement.

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