Title
Functional thiamine deficiency in end-stage renal disease: malnutrition despite ample nutrients

Journal
Kidney International, 90(2)

ISSN
0085-2538

Authors
Moradi, Hamid
Said, Hamid M

Publication Date
2016-08-01

DOI
10.1016/j.kint.2016.04.017

Peer reviewed

HHS Public Access

Author manuscript

Kidney Int. Author manuscript; available in PMC 2017 July 20.

Published in final edited form as:

Kidney Int. 2016 August ; 90(2): 252–254. doi:10.1016/j.kint.2016.04.017.

Functional thiamine deficiency in end-stage renal disease: malnutrition despite ample nutrients

Hamid Moradi and **Hamid M. Said**

Long Beach VA Healthcare System, Long Beach, California; Division of Nephrology, University of California, Irvine, Irvine, California, USA

Abstract

Zhang *et al.* found that plasma concentrations of the thiamine antimetabolite oxythiamine are significantly increased in patients with end-stage renal disease. These investigators discuss the potential sources of oxythiamine and the consequences of its plasma elevation. This commentary addresses the significance of these findings and expands on the potential role of gut microbiome in the generation of this antithiamine metabolite.

It is well-known that kidney disease is associated with mitochondrial dysfunction, abnormal energy production, and metabolism.[1] Mitochondrial damage and impaired function also lead to oxidative stress and subsequent inflammation, which are part and parcel of chronic kidney disease. Therefore, it is not surprising that end-stage renal disease (ESRD) is associated with protein-energy wasting, inflammation, oxidative stress, and sarcopenia. Furthermore, patients with ESRD have a significantly increased risk of mortality, with half of these deaths attributed to cardiovascular disease (CVD). The main contributors to this enormous CVD risk have not been clearly identified, and, in fact, traditional risk factors such as hypercholesterolemia and obesity are paradoxically associated with better survival in large epidemiologic studies of hemodialysis patients. It has been suggested that nontraditional risk factors such as malnutrition, uremic toxins, inflammation, and oxidative stress most likely play a more prominent role than conventional risk factors in ESRD-associated morbidity and mortality.

In this regard, there has been much interest in the evaluation of nutrition and nutritional status of patients with ESRD and their potential impact on outcomes. Most clinical studies evaluating the nutritional status of a patient rely on serum levels of micronutrients. Yet in the field of nutrition, there is increasing realization that the serum/environmental presence of vitamins and micronutrients does not necessarily reflect adequacy and content at the tissue and cellular levels. This is because cellular nutrition is not only determined by the presence of micronutrients in the serum/media, but also by the normal uptake of these nutrients into the cell and their efficient utilization at the tissue level. In fact, there are scenarios in which a patient can have functional deficiency of a vitamin or nutrient despite normal serum content.

Correspondence: Hamid M. Said, 5901 East 7th Street, Long Beach, CA 90822, USA. hmsaid@uci.edu.

DISCLOSURE

All the authors declared no competing interests.

For example, in thiamine-responsive megaloblastic anemia, an autosomal recessive disorder caused by mutations in the gene *SLC19A2* (which encodes thiamine transporter-1), there is decreased thiamine uptake in tissues that rely heavily on thiamine transporter-1, including inner hair cells of the cochlea, hematopoietic cells, and β-islet cells of the pancreas. Hence, despite having normal serum thiamine levels, patients with thiamine-responsive megaloblastic anemia exhibit megaloblastic anemia, diabetes mellitus, and sensorineural deafness. In addition, processes that interfere with cellular metabolism and utilization of vitamins can also lead to the pathogenesis of vitamin deficiency despite normal serum levels. These mechanisms can lead to a state of functional vitamin deficiency despite adequate intake and the presence of micronutrients. There is now accumulating evidence that such mechanisms may be at play with regard to thiamine in patients with ESRD.

Thiamine (vitamin B_1) is a water-soluble vitamin belonging to the B-complex family, the deficiency of which has been closely linked with various clinical abnormalities including neurologic disease and CVD.[2] Thiamine acts as a coenzyme in a number of essential metabolic processes including the pentose phosphate pathway and carbohydrate metabolism. It is a key coenzyme for the mitochondrial pyruvate dehydrogenase and α-ketoglutarate dehydrogenase, 2 enzymes that play a vital role in the production of adenosine triphosphate. Aside from energy production, thiamine deficiency can lead to mitochondrial dysfunction and generation of oxygen free radicals. Furthermore, thiamine plays a critical role in the production of reduced NAD phosphate, an important reducing agent the deficiency of which can further exacerbate oxidative stress. Thiamine is regarded as an essential vitamin given that humans lack the machinery needed to synthesize it and must obtain thiamine from exogenous sources. Previously, it was thought that dietary intake of foods rich in thiamine (i.e., unrefined cereal grains, nuts, legumes, and peas) is the only source of this vitamin for humans; however, it is now becoming clear that bacterial microflora of the colon are capable of producing thiamine and that some of this thiamine can be absorbed. The gastrointestinal absorption of dietary and microbiota-produced thiamine is facilitated by a carrier-mediated transport system via thiamine transporter-1 and thiamine transporter-2. These transporters are also expressed in a variety of organs including the kidney, liver, and heart where they play a major role in thiamine uptake into cells before it can be utilized. In fact, tissue-specific (i.e., localized) deficiency of thiamine has been described in humans in disorders such as thiamine-responsive megaloblastic anemia. Interestingly, we previously showed decreased expression of thiamine transporter-1 and thiamine transporter-2 in several organs in an animal model of chronic kidney disease (5/6 nephrectomy).[3]

It has long been shown that patients with ESRD on dialysis have significantly reduced transketolase activity.[4] The latter is a thiamine-dependent enzyme that is a major step in the pentose phosphate pathway. Dysfunctional transketolase activity can lead to a myriad of abnormalities including mitochondrial dysfunction, oxidative stress, and the development of neurologic abnormalities similar to those experienced by some patients with ESRD. It was also demonstrated that serum from dialysis patients inhibits the pentose phosphate pathway and transketolase activity despite normal or increased levels of serum thiamine. Therefore, it is commonly acknowledged that uremic toxin(s) accumulating in patients with ESRD causes inhibition of transketolase activity, hence causing functional thiamine deficiency. The identity of the toxin(s) causing this abnormality was not definitively determined until the

recent study by Zhang *et al.*[5] (2016) that showed that plasma concentrations of oxythiamine, a well-known thiamine antagonist and inhibitor of transketolase, are significantly increased in patients with ESRD. Using liquid chromatography and mass spectrometry, Zhang *et al.* analyzed plasma samples from patients with ESRD on hemodialysis and peritoneal dialysis and compared the results with those of healthy control subjects. They found that oxythiamine concentrations are increased 15-fold in hemodialysis patients and 4-fold in patients on peritoneal dialysis. Furthermore, they found that inhibition of transketolase activity relies on conversion of oxythiamine to oxythiamine pyrophosphate. Erythrocyte levels of oxythiamine pyrophosphate increased 4-fold in patients on hemodialysis compared with control subjects. In addition, plasma concentrations of oxythiamine correlated significantly with erythrocyte oxythiamine pyrophosphate levels, and erythrocyte oxythiamine pyrophosphate levels in turn significantly and negatively correlated with transketolase activity.

The authors contend that because incubation of erythrocytes from dialysis patients with strikingly increased concentrations of thiamine (500-fold higher than physiologic levels) restored transketolase activity, pharmacologic doses of thiamine should be considered a therapeutic option for dialysis-related functional thiamine deficiency. However, it should be noted that plasma concentrations of thiamine were already 6- to 10-fold higher in patients with ESRD compared with healthy control subjects. In addition, it is not known whether long-term heavy thiamine supplementation at pharmacologic doses would lead to adverse side effects in patients with ESRD who lack renal clearance of this vitamin and its byproducts. A more plausible alternative would be to prevent the production and excess absorption of oxythiamine. In this regard, the authors maintain that the most likely source of oxythiamine is dietary intake of acidic foods rich in thiamine that have been cooked at high temperatures. Via this mechanism, thiamine is converted to oxythiamine and its absorption and decreased renal clearance in ESRD lead to elevated serum levels. Although this is a distinct possibility, an intriguing alternative explanation would be increased production of oxythiamine by gut microflora in patients with ESRD. There are numerous reports linking changes in bowel microbiota with the production of metabolites from various dietary nutrients that can lead to obesity and CVD.[6, 7] For example, Wang *et al.*[6] demonstrated that intestinal microflora can metabolize phosphatidylcholine to metabolites such as trimethylamine N-oxide, which can go on to cause CVD. In another study, Koeth *et al.*[7] found that intake of L-carnitine (in red meat) can cause atherosclerosis via a similar mechanism. Therefore, these authors have identified gut microbiota as a link between dietary intake of nutrients and CVD. Furthermore, it is well-known that dietary and environmental factors can lead to alterations in intestinal microbiome, thereby contributing to the pathogenesis of various clinical phenotypes. In fact, Vaziri *et al.*[8] evaluated the microbiota of patients with ESRD on hemodialysis using phylogenetic microarray and found significant differences in the abundance of numerous families of bacteria between the ESRD and control groups. Furthermore, there is a report of a specific form of *Escherichia coli* ("thiamine-less" mutant *E coli)* that can convert oxythiamine to thiamine.[9] Therefore, it is conceivable that other classes of bacteria can exist in the gut that can mediate the reverse process and produce oxythiamine. An intriguing possibility may be that altered gut microflora in ESRD can lead to abnormal oxythiamine production and absorption with

subsequent functional thiamine deficiency in the face of normal or increased serum levels. Although overt symptoms and signs of B_1 deficiency might not be present, functional thiamine deficiency may contribute to various complications of ESRD including oxidative stress, impaired energy metabolism, anemia, CVD, and ultimately increased mortality (Figure 1). These novel mechanisms will need to be further examined in future studies.

Acknowledgments

HM is supported by a career development award from the Office of Research and Development of the Department of Veterans Affairs 1 IK CX 001043-01A2. HMS is supported by funding from National Institutes of Health grant DK56061-17.

References

1. Zhan M, Brooks C, Liu F, et al. Mitochondrial dynamics: regulatory mechanisms and emerging role in renal pathophysiology. Kidney Int. 2013; 83:568–581. [PubMed: 23325082]
2. Said HM. Intestinal absorption of water-soluble vitamins in health and disease. Biochem J. 2011; 437:357–372. [PubMed: 21749321]
3. Bukhari FJ, Moradi H, Gollapudi P, et al. Effect of chronic kidney disease on the expression of thiamin and folic acid transporters. Nephrol Dial Transplant. 2011; 26:2137–2144. [PubMed: 21149507]
4. Lonergan ET, Semar M, Sterzel RB, et al. Erythrocyte transketolase activity in dialyzed patients. A reversible metabolic lesion of uremia. N Engl J Med. 1971; 284:1399–1403. [PubMed: 4325316]
5. Zhang F, Masania J, Anwar A, et al. The uremic toxin oxythiamine causes functional thiamine deficiency in end-stage renal disease by inhibiting transketolase activity. Kidney Int. 2016; 90:396–403. [PubMed: 27198804]
6. Wang Z, Klipfell E, Bennett BJ, et al. Gut flora metabolism of phosphatidylcholine promotes cardiovascular disease. Nature. 2011; 472:57–63. [PubMed: 21475195]
7. Koeth RA, Wang Z, Levison BS, et al. Intestinal microbiota metabolism of L-carnitine, a nutrient in red meat, promotes atherosclerosis. Nat Med. 2013; 19:576–585. [PubMed: 23563705]
8. Vaziri ND, Wong J, Pahl M, et al. Chronic kidney disease alters intestinal microbial flora. Kidney Int. 2013; 83:308–315. [PubMed: 22992469]
9. Fukui S, Ohishi N, Kishimotostakamizaw A, Hamazima Y. Formation of “thiaminosuccinic acid” as an intermediate in the transformation of oxythiamine to thiamine by a thiamineless mutant of Escherichia coli. J Biol Chem. 1965; 240:1315–1321. [PubMed: 14284742]

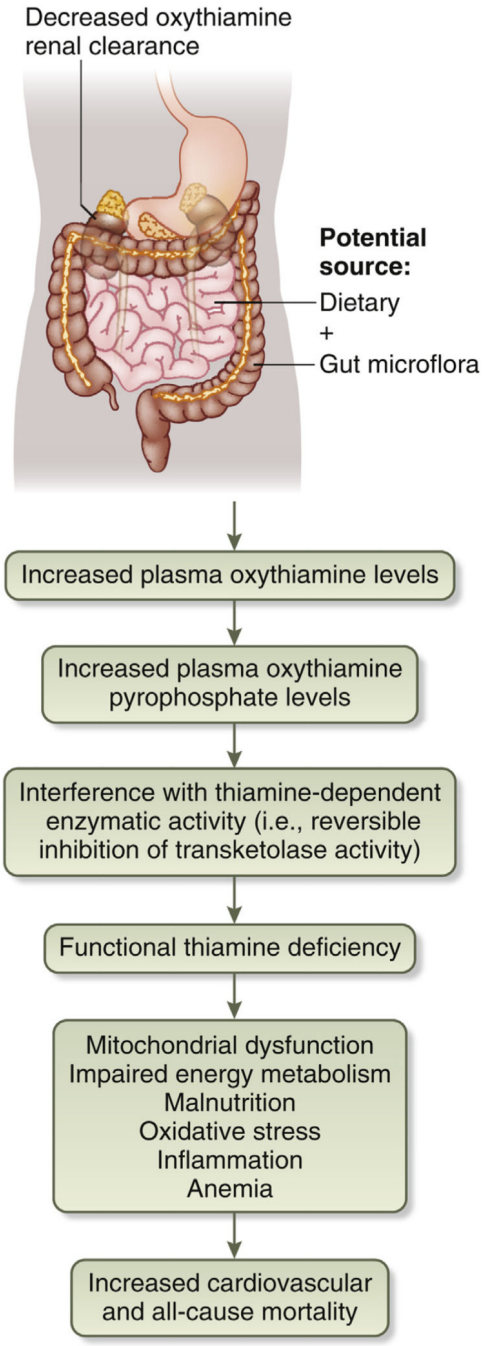

Figure 1.
Potential sources of oxythiamine and consequences of functional thiamine deficiency in end-stage renal disease.