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Thiamin Status and Supplementation in the Management of Diabetes Mellitus and its Vascular Comorbidities

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Abstract

The water soluble B vitamin, thiamin, in its coenzyme form as thiamin pyrophosphate (TPP), is necessary for key reactions in glucose metabolism. For this reason, associations between thiamin status or thiamin supplementation and diabetes have been the focus of recent research. Currently, it is not clear how occurrence of diabetes relates to parameters of thiamin status, such as plasma thiamin levels. However, there is strong evidence that the diabetic state increases urinary thiamin excretion and decreases the activity of transketolase (TK), a TPP-dependent enzyme of the hexose monophosphate (HMP) shunt in various body tissues. Impairment of TK activity and subsequent down-regulation of the HMP shunt activates several pathways that contribute to vascular damage and development of diabetes-related comorbidities such as retinopathy, cardiomyopathy, and nephropathy. Thiamin supplementation has been shown to be effective in restoring TK activity in animal models of diabetes, and in type 1 and type 2 diabetic individuals. Thiamin supplementation has also been shown to be effective in preventing or reversing, either partially or completely, hyperglycemia-induced damage to vascular endothelial cells, and microalbuminuria associated with diabetic nephropathy. Here, we review from current literature examining the relationship between diabetes and thiamin status as well as intervention trials evaluating the effect of thiamin supplementation on glycemic control and prevention of vascular comorbidities of diabetes.

Keywords: thiamin; benfotiamine; diabetes; transketolase; diabetic nephropathy; fractional excretion of thiamine; diabetic comorbidities

Introduction

Thiamin: discovery, structure, function, deficiency, and nutritional status

Thiamin, also known as vitamin B1, is a water soluble vitamin found in moderate to high quantities in whole and enriched grain products, lean meats (especially lean pork), organ meats, eggs, nuts, and seeds [1]. In 1897, the Dutch physician Christiaan Eijkman observed that chicks fed polished rice, rather than unrefined rice, developed a syndrome called polyneuritis, characterized by paralysis and inability to walk [2]. Eijkman and his associate Gerrit Grijns determined that the rice polishings removed during grain refinement contained an essential nutrient that was distinct from macronutrients. In 1911, the Polish biochemist Casimir Funk isolated the "anti-polyneuritis factor" from rice bran [2,3]. In 1934, Robert Williams elucidated the structure of thiamin and showed that it consists of a pyrimidine ring linked via a methylene bridge to a thiazole ring with methyl and hydroxyethyl side groups [3]. Thiamin is found in the body in three different phosphate ester forms: thiamin monophosphate (TMP), thiamin pyrophosphate (TPP), and thiamin triphosphate (TTP), with TPP acting as the metabolically active coenzyme form. Thiamin is digested into its free form and is absorbed in the ileum and jejunum via carrier-mediated transport using thiamin transporter-1 (THTR-1) and thiamin transporter-2 (THTR-2) [4]. At pharmacological doses, thiamin can also be absorbed in the small intestine via passive diffusion [5]. The majority of thiamin (approximately 80-90%) is transported in the blood as TPP in erythrocytes (RBCs). The remainder is transported bound to albumin and thiamin binding protein. THTR-1 and THTR-2 are responsible for cellular uptake of thiamin [4]. About 80% of intracellular thiamin is in the phosphorylated form with the highest concentrations of thiamin occurring in the brain, skeletal muscle, heart, liver, and kidneys. Thiamin is essential for the metabolism of lipids, amino acids, and carbohydrates as well as activation of ion channels in nerve membranes, production of pentose sugars and NADPH [6,7]. TPP serves as a coenzyme for pyruvate dehydrogenase complex, the alpha-ketoglutarate dehydrogenase complex, and transketolase (TK), the rate-limiting enzyme of the reversible non-oxidative branch of the hexose monophosphate shunt (HMP shunt). TPP is also a cofactor for the branched-chain α-keto acid dehydrogenase complex, necessary for the catabolism of the branched-chain amino acids valine, leucine, and isoleucine, as well as acyl CoA dehydrogenase, which catalyzes the initial step of fatty acid β-oxidation [7]. The RDA for thiamin is 1.2 mg/day for adult males, 1.1 mg/day for adult females, and 1.4 mg/day during pregnancy and lactation [1]. Thiamin deficiency can be caused by inadequate intake (common in developing nations where refined grain products are not fortified), alcoholism (the most common cause of thiamin deficiency in the United States), and excessive intake of thiaminase-containing foods such as raw shellfish, fish paste, ferns, or foods containing anti-thiamin factors including tea, coffee, and betel nuts [1,8]. Thiamin deficiency results in a condition called beriberi, with dry beriberi affecting the nervous system. Symptoms include paralysis, difficulty walking, tingling, muscle atrophy, mental confusion, speech difficulties, and nystagmus. Symptoms of wet beriberi, which affects the cardiovascular system, are cardiomegaly, dyspnea, tachycardia, and lower extremity edema [9]. Because alcohol inhibits the thiamin transporters in the small intestine, excessive alcohol intake can lead to a thiamin deficiency disorder known as Wernicke-Korsakoff syndrome, characterized by mental confusion, disorientation, memory loss, opthalmoplegia, and possibly coma and death [9,10]. Thiamin status can be assessed via measurements of serum or RBC thiamin levels, measurement of urinary excretion of thiamin and its metabolites, or determination of RBC TK activity (also known as thiamin effect) [11]. Because serum and RBC thiamin, and thiamin excretion do not accurately reflect total body thiamin stores, assays

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measuring thiamin effect have been used. The thiamin effect assays the increase in TK activity with addition of TPP in an *ex vivo* blood assay. Thiamin deficiency is indicated by an increase of ≥ 15% in TK activity with exogenous TPP [12]. Because thiamin, as TPP, is necessary for glucose metabolism and maintenance of glycolysis, TCA cycle, and HMP shunt, several studies have investigated the impact of the diabetic state on thiamin status as well as how thiamin supplementation may affect thiamin status, glycemic control, and vascular health in diabetic individuals.

Diabetes and thiamin status

Several lines of evidence suggest that the diabetic state negatively affects thiamin status via hyperglycemia-induced suppression of thiamin transporters responsible for thiamin reuptake in renal proximal tubules [12-16]. Babaei-Jadidi et al. showed that streptozocin (STZ)-induced diabetic rats had significantly higher rates of urinary thiamin excretion than control rats, and this led to plasma thiamin concentrations that were 48-69% lower in the diabetic rats [12]. Kohda et al. found similar decreases in plasma thiamin levels in STZ-induced diabetic mice and rats [17]. Suppression of thiamin status appears to be corrected with supplementation with either thiamin or benfotiamine (S-benzoylthiamin monophosphate, a highly bioavailable lipid-soluble thiamin derivative) [12,17]. It is important to note that despite decreased plasma thiamin levels and suppressed TK activity, STZ-induced diabetic rats were not thiamin deficient as determined by the thiamin effect [12,17]. Further, glomerular TK activity was 24-29% lower in STZ-induced diabetic rats than in control rats. Suppressed TK activity was associated with a decreased concentration ratio of ribose 5-phosphate (R5P) to glyceraldehyde 3-phosphate (GA3P), suggesting down-regulation of the HMP shunt [12]. Supplementation with either thiamin or benfotiamine increased TK activity to above-baseline levels and also increased the R5P/GA3P concentration ratio [12,18]. Though clinical studies have provided inconsistent results regarding the effect of diabetes on plasma thiamin levels, several studies demonstrate an increased thiamin excretion in the diabetic state (Table 1) [13-15]. Plasma and RBC thiamin levels, and RBC TK activity did not vary significantly between healthy subjects and subjects with type 2 diabetes with varying degrees of albuminuria. However, fractional excretion of thiamin ($FE_{thiamin}$) was significantly higher in diabetic subjects (22.8% for control vs. 33.5% for type 2 DM) [13]. $FE_{thiamin}$, a marker of renal mishandling of thiamin, can result from diabetes-induced suppression of renal thiamin uptake, secondary to decreased expression of thiamin transporters THTR-1 and THTR-2 in renal proximal tubules [12,13,15,16]. In addition, among diabetic subjects, $FE_{thiamin}$ excretion percentage was positively correlated with hemoglobin A_{1c} [13].

Two other clinical studies have found an association between type 1 and type 2 diabetes with increased urinary thiamin excretion as well as with impaired thiamin status (Table 1) [14,15]. Al-Attas et al. observed significantly lower estimates of total thiamin and significantly higher urinary thiamin clearance in subjects with type 1 and type 2 diabetes [14]. Thornalley et al. found $FE_{thiamin}$ excretion to be 25 times higher in subjects with type 1 diabetes and 15 times higher in subjects with type 2 diabetes when compared against healthy controls (2.8% for control *vs.* 71.2% for type 1 DM and 41.6% for type 2 DM) [15]. Additionally, renal clearance of thiamin was 24 times higher in type 1 diabetic patients and 16 times higher in type 2 diabetic patients when compared with controls (3.7 ml/min for control vs. 86.5 ml/min for type 1 DM and 59.8 ml/min for type 2 DM). Furthermore, plasma thiamin levels were 76% lower in subjects with type 1 diabetes and 75% lower in subjects with type 2 diabetes when compared against healthy controls (64.1 ± 12.0 nmol/L for control vs. 15.3 ± 9.6 nmol/L for type 1 DM and 16.3 ± 11.5 nmol/L for type 2 DM, $p<0.001$) [15]. However, no patient was thiamin deficient as determined by the thiamin effect, and RBC thiamin concentrations were similar among all three groups [15]. Normal RBC thiamin levels and lack of thiamin effect despite suppressed plasma levels appears to be due to increased expression of thiamin transporters THTR-1 and reduced folate carrier (RFC-1) on RBCs in diabetic subjects; and suppressed plasma thiamin levels are the result of decreased renal reuptake of thiamin as evidenced by increased $FE_{thiamin}$ excretion in diabetic subjects [13,15]. However, studies have shown that thiamin uptake and TK activity were decreased in the diabetic state in the renal glomeruli, retina, and peripheral nerves, which can lead to vascular damage [12,15,18-20].

Thiamin supplementation and glycemic control

In STZ-induced diabetic animal models, benfotiamine or thiamin supplementation alone without any other treatment was shown to be ineffective in normalizing plasma glucose levels or HbA_{1c} [12,17,21]. However, according to the results of a recent study, benfotiamine supplementation in conjunction with insulin therapy may be a promising regimen for glycemic control [18]. STZ-induced hyperglycemic mice were treated with a transplant of bone marrow-derived insulin-producing cells (BM-derived IPCs) alone, benfotiamine alone (40 mg/kg), or a combination. Benfotiamine treatment had no significant effect on blood glucose levels in non-transplanted mice (467.1 ± 43.3 mg/dL with benfotiamine vs. 446.4 ±38.9 mg/dL without benfotiamine). After transplantation with BM-derived IPCs, blood glucose levels decreased significantly to a mean of 185.1 ± 20 mg/dL within a few days, and administration of benfotiamine allowed for further significant decreases in blood glucose levels to a mean of 127.8 ± 17.1 mg/dL within 3 hours of administration. In addition, benfotiamine treatment before an oral glucose challenge (1 g/kg) in normal mice without STZ-induced hyperglycemia allowed for more rapid normalization of blood glucose levels. Sixty minutes following the glucose challenge, blood glucose levels were significantly lower in the benfotiamine group than in the non-treatment group (124.7 ± 5.1 mg/dL vs 158.7 ± 6.2 mg/dL), suggesting that benfotiamine supplementation

Authors	Subjects	Thiamin Status	Diabetes
Adaikalakoteswari et al. [13]	T2DM: n=115 Control: n=37	No differences in plasma thiamin levels or RBC thiamin levels Increased urinary excretion of $FE_{thiamin}$ in T2DM	T2DM with varying degrees of renal function
Thornalley et al. [15]	T1DM: n=26 T2DM: n=48 Control: n=20	Plasma thiamin levels were decreased 76% in T1DM and 75% in T2DM Urinary thiamin excretion 4 times higher in T1DM and 3 times higher in T2DM	T1DM or T2DM with varying degrees of renal function Mean HbA_{1c}=8.6-8.7%
Al-Attas et al. [14]	T2DM: n=162 T1DM: n=43 Control: n=26	Estimates of total thiamin significantly lower in T2DM and T1DM Urinary thiamin excretion significantly higher in T2DM and T1DM	T2DM or T1DM with varying degrees of renal function
Wong et al. [35]	T2DM: n=88 Control: n=91	Higher thiamin intake associated with higher levels of EPCs and higher FMD in diabetic subjects only	Mean HbA_{1c}=7.64 ± 0.13%

Table 1: Summary of clinical studies examining thiamin status in type 1 (T1DM) or type 2 diabetes (T2DM). $FE_{thiamin}$: fractional excretion of thiamin; EPC: endothelial progenitor cells; FMD: flow-mediated dilation

provided immediate assistance in glycemic control but only when insulin was present [18]. Human intervention trials have provided conflicting results on the effectiveness of thiamin supplementation on glycemic control. Gonzalez-Ortiz et al. found that supplementation with thiamin (150 mg/d) for 1 month significantly decreased plasma glucose concentrations from baseline in type 2 diabetic subjects (6.0 ± 0.9 mmol/l vs. 6.7 ± 1.0, p=0.024) [22]. The subjects of this study had fairly good glycemic control at baseline (mean HbA_{1c} of 6.3 ± 0.8% in placebo group and 6.3 ± 0.3% in treatment group) and were receiving no pharmacological diabetic therapy. Thus, it appears that these subjects had well-controlled type 2 diabetes mellitus [22]. In a separate study, supplementation with 50 mg benfotiamine daily for 3 months in type 1 diabetic children had no significant independent effect on HbA_{1c} levels when compared to placebo [23]. However, these subjects had poorer glycemic control at baseline (mean HbA_{1c} of 8.8 ± 0.5% in placebo group and 9.2 ± 0.5% in treatment group) which may account, at least in part, for the variability of findings [23].

Thiamin supplementation and prevention of vascular comorbidities

Results from animal models and intervention trials have suggested that thiamin supplementation may aid in prevention or regression of diabetic vascular comorbidities, especially nephropathy (Table 2). Either 7 mg/kg or 70 mg/kg of either benfotiamine or thiamin with moderate insulin therapy in STZ-induced diabetic rats decreased development of microalbuminuria by 70-80% as compared to no treatment in diabetic rats (p<0.01). Benfotiamine and thiamin were equally efficacious in achieving this result. A similar pattern was seen in regards to development of proteinuria [12]. In a human intervention trial, Alkhalaf et al. [24] evaluated subjects with type 2 diabetes and diabetic nephropathy as indicated by urinary albumin excretion (UAE) of 15-300 mg/24 h or an equivalent albumin-to-creatinine ratio of 1.25-25 in males and 1.75-35 in females. Supplementation with benfotiamine (300 mg, 3 times daily for 12 weeks) improved thiamin status. However, there were no changes in 24-hr UAE or 24-hr KIM-1 (kidney injury molecule-1, a marker of renal tubular damage) excretion with supplementation. However, subjects had fairly advanced nephropathy at baseline (a mean UAE of 90 mg/24 hr in the benfotiamine group and 97 mg/24 hr in the placebo group), which may have precluded any possible beneficial effect of benfotiamine supplementation [24]. A separate study evaluated type 2 diabetic patients, who also presented with microalbuminuria, but overall had less advanced diabetic nephropathy at baseline (a mean UAE of 43.7 mg/24 hr in the thiamin group and 50.9 mg/24 hr in the placebo group) [25]. In this study, thiamin supplementation (100 mg, thiamin 3 times daily for 3 months) had no effects on glycemic control. However, UAE significantly decreased from baseline in subjects receiving thiamin supplementation (-17.7 mg/24 hr, p<0.001) while there were no significant changes in the placebo group, suggesting that thiamin supplementation promotes regression of microalbuminuria [25]. Benfotiamine supplementation may provide benefits in the prevention of other diabetes-related vascular comorbidities, including cardiomyopathy and retinopathy. Benfotiamine supplementation for 14 weeks (100 mg/kg/day) in STZ-induced diabetic mice completely corrected hyperglycemia-induced disruptions in calcium homeostasis and mechanical functioning of cardiomyoctyes [21]. Additionally, STZ-induced diabetic rats showed significant increases in expression of brain natriuretic peptide (BNP), a marker for heart failure, but thiamin repletion almost completely reversed BNP elevations. In the same animal model, thiamin supplementation prevented the formation of cardiac fibrosis observed in STZ-induced diabetic rats that did not receive supplementation [17]. A small human intervention trial showed normalization in hyperglycemia-induced increases in levels of angiopoietin-2 within 2 weeks of supplementation with benfotiamine (300 mg, 2 times a day) and α-lipoic acid (600 mg, twice a day) in type 1 diabetic subjects. Within 4 weeks, benfotiamine plus α-lipoic acid also normalized diabetes-induced decreased activity of prostacyclin synthase, an anti-atherogenic enzyme associated with the endothelium [26]. Further, results of this study showed two- to-threefold increases in monocyte TK activity from baseline after two weeks of benfotiamine supplementation [26]. In type 1 and type 2 diabetic subjects, plasma thiamin levels were negatively correlated with plasma levels of soluble-vascular adhesion molecule-1 (sVCAM-1), a marker of endothelial cell dysfunction associated with both microvascular and macrovascular comorbidities in diabetes [15,27-30]. Thiamin status in diabetic individuals may also be correlated to levels of circulating endothelial progenitor cells (EPC), which are needed for synthesis of new endothelial tissue [31]. Studies have shown that EPC levels decrease with diabetes and that this reduction may play a role in development of micro- and macro-vascular comorbidities [32-34]. Consistent with those findings, type 2 diabetic subjects demonstrated significantly

Author	Subjects	Findings
Gonzalez-Ortiz et al. [22]	T2DM, well-controlled Thiamin (150 mg/d): n=12 Placebo: n=12	Thiamin supplementation for 1 month significantly decreased plasma glucose concentrations from baseline
Valerio et al. [23]	Children with T1DM Benfotiamine 50 mg/d: n=5 Placebo: n=5	Benfotiamine supplementation had no significant independent effect on HbA_{1c} levels
Alkhalaf et al. [24]	T2DM Benfotiamine (900 mg/d): n=39 Placebo: n=43	Benfotiamine supplementation had no effect on UAE or KIM-1 excretion in diabetic nephropathy
Rabbani et al. [25]	T2DM with microalbuminuria Thiamin 300 mg/d: n=20 Placebo: n=20	Thiamin supplementation for 3 months decreased 24-hr UAE
Du et al. [26]	Benfotiamine (600 mg/d) plus α-lipoic acid (1200 mg/d) T1DM: n=9 Nondiabetic control: n=12	Benfotiamine supplementation alone increased monocyte TK activity twofold to three fold within 2 weeks Within 2 weeks, benfotiamine normalized diabetes-induced elevation of angiopoietin-2 levels Within 4 weeks, benfotiamine normalized diabetes-induced suppression of prostacyclin synthase

Table 2: Summary of intervention trials with thiamin or benfotiamine, a highly bioavailable lipid-soluble thiamin derivative. UAE: urinary albumin excretion; KIM-1: kidney injury molecule-1; TK: transketolase

lower levels of circulating EPCs as compared to healthy controls [35]. In diabetic subjects (but not controls), increased dietary thiamin intake was significantly correlated with higher levels of circulating EPCs and flow-mediated dilation (FMD) of the brachial artery [35].

Potential mechanisms

There is sufficient evidence to indicate that thiamin transporters and TK activity are suppressed in diabetes [12,13,15,18-20]. Suppressed TK activity can lead to accumulation of GA3P, fructose-6-phosphate (F6P), and dihydroxyacetone phosphate (DHAP) [12,18]. Because these are also intermediates of early stage glycolysis, their accumulation is exacerbated by hyperglycemia-induced mitochondrial free radical production, which inhibits the glycolytic enzyme glyceraldehyde phosphate dehydrogenase (GAPDH) [18,35]. At abnormally elevated levels, GA3P, F6P, and DHAP can potentially initiate hyperglycemia-induced pathways that lead to vascular damage, including the protein kinase C pathway (PKC), the advanced glycation end products (AGE) pathway, the hexosamine biosynthesis pathway (HBP), and the dicarbonyl compounds pathway [12,17,18,26,36,37]. The PKC pathway increases vascular permeability by activating vascular endothelial growth factor and stimulates vascular thrombosis by increasing expression of plasminogen activator inhibitor (PAI)-1 [12,17]. Activation of AGE receptors (RAGE), found on glomerular endothelial cells, cardiomyocytes, pericytes, and podocytes, stimulates postreceptor signaling, intracellular reactive oxygen species formation, and altered gene expression, leading to vascular damage [12,21,26]. In the renal glomeruli, RAGE activation increases growth factor expression, resulting in expansion of mesangial cells, necrosis of glomerular tissue, and ultimately nephropathy [12]. The dicarbonyl compounds pathway, which utilizes the dicarbonyl compounds methylglyoxal, glyoxal, and 3-deoxyglucosone, leads to further AGE formation and has also been associated with development of diabetic nephropathy and cardiomyocyte damage [12,21]. HBP activation contributes to hyperglycemia-induced vascular damage by increasing expression of PAI-1 and transforming growth factor-β1 [17]. Thus, suppression of TK activity and subsequent accumulation of GA3P, F6P, and DHAP appear to play major roles in the development of vascular comorbidities of diabetes. Restoring TK activity via benfotiamine or thiamin supplementation can increase the flux of glucose into HMP shunt, and also increase flux of GA3P, F6P, and DHAP into HMP shunt and away from hyperglycemia-induced pathways that lead to vascular damage [12,18,21,26]. Animal studies have shown that either benfotiamine or thiamin supplementation in the diabetic state decreases hyperglycemia-induced PKC and HBP activity as well as concentrations of dicarbonyl compounds, AGEs, and PAI-1 [12,17,38,39]. Regression of damage to glomerular endothelial cells, podocytes, and pericytes appears to restore the function of these cells, decrease UAE, and reverse diabetes-induced microalbuminuria [25,40]. A small human intervention trial showed normalization in hyperglycemia-induced increases in levels of angiopoietin-2 with benfotiamine plus α-lipoic acid supplementation for 2 weeks in type 1 diabetic subjects. Benfotiamine plus α-lipoic acid also decreased diabetes-induced elevations in hexosamine pathway activity by 40% [26]. In addition to its preventive effect on diabetic nephropathy and cardiomyopathy, thiamin supplementation has been shown to be protective against other vascular comorbidities such as retinopathy. *In vitro*, thiamin and benfotiamine have been shown to completely prevent hyperglycemia-induced apoptosis of human retinal capillary pericytes, which coordinate with endothelial cells to direct vascular function [41].

Conclusions

The diabetic state suppresses expression of the thiamin transporters THTR-1 and THTR-2 in renal proximal tubules, potentially decreasing renal reabsorption of thiamin [12-15]. Although the impact of this mechanism on several parameters of thiamin status (including plasma thiamin levels and RBC thiamin concentrations) is unclear, a growing body of evidence suggests that diabetes is associated with suppressed TK activity in a wide variety of body tissues [12-15,26]. Thus, a suppression of TK activity, and subsequent down-regulation of the HMP shunt, resulting in accumulation of GA3P, F6P, and DHAP may be at least one mechanism in the development of diabetes-induced vascular damage and other comorbidities [12,17,18,26,36,37]. Although thiamin supplementation and restoration of TK activity may not contribute to an improvement in glycemic control in diabetic individuals [12, 17,21,23], it does appear to prevent, as well as, partially or completely, reverse diabetic nephropathy, and possibly cardiomyopathy and retinopathy [12,17,21,25,26]. Thus, while thiamin deficiency does not appear to be a factor in the development of diabetes, and although it remains unclear whether diabetes promotes thiamin deficiency, it may be important to assess thiamin status in individuals with diabetes. Additional studies evaluating potential benefits of thiamin or benfotiamine supplementation for diabetes and its associated comorbidities may be needed to validate clinical findings.

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