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**Thiamine deficiency in diabetes mellitus and the impact of thiamine on glucose metabolism and vascular disease**

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# Thiamine deficiency in diabetes mellitus and the impact of thiamine replacement on glucose metabolism and vascular disease.

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## Disclosures

None

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**Background:** Despite the targeting of traditional risk factors for cardiovascular disease, disease burden has not been completely eliminated. Thiamine is an essential cofactor in carbohydrate metabolism and individuals with diabetes are thiamine deficient. The pathophysiology of recognised complications of thiamine deficiency is similar to that underlying atherosclerosis and the metabolic syndrome, namely oxidative stress, inflammation and endothelial dysfunction.

**Aims:** This review examines the mechanisms by which thiamine deficiency occurs in individuals with diabetes, how this deficiency leads to hyperglycaemic-induced damage, and the effect of thiamine replacement on vascular disease, endothelial function and oxidative stress.

**Conclusions:** Thiamine administration can prevent the formation of harmful by-products of glucose metabolism, reduce oxidative stress and improve endothelial function. The potential benefit of long-term replacement in those with diabetes is not yet known but may reduce cardiovascular risk and angiopathic complications.

### Review criteria

A literature search was performed from the PubMed database using the words thiamine, diabetes, endothelial function, oxidative stress and inflammation.

### Message for the clinic

Current targets for prevention of vascular disease have reduced, but not eliminated, the disease burden of diabetes. Other nutritional and metabolic factors may be implicated in their development, of which thiamine deficiency is a possibility.

## Introduction

The pathogenesis of vascular complications in diabetes is a much debated subject and despite extensive research no unifying mechanism has been discovered. Several hypotheses exist: capillary hypertension, insulin resistance syndrome, endothelial dysfunction, increased vascular inflammation and oxidative stress with advanced glycation end product (AGE) formation. While these are all important processes it would appear that one is not exclusive of the other and it is more likely that all the above processes are integrally related. Figure 1 shows the relationship between these processes and how they act synergistically to promote the development of diabetes and vascular disease. Current therapies not only target traditional cardiovascular risk factors such as dyslipidaemia and hypertension but novel risk factors such as oxidative stress, endothelial dysfunction and inflammation. Thiamine is an example of a treatment that is known to affect these novel processes but with little evidence as to how it affects cardiovascular risk. This article aims to review the way in which thiamine deficiency occurs in diabetes and how replacement may lead to changes in vascular risk and vascular disease.

## Thiamine

Thiamine is a member of the B-vitamin family and was the first water-soluble vitamin to be discovered in 1912 and isolated in 1926. Humans cannot synthesize thiamine and so a regular intake of thiamine, from exogenous sources, yeasts and plants, is necessary to maintain body stores and the recommended daily intake for adults is between 1 and 1.4 mg/day.

Thiamine is absorbed from the diet in the proximal part of the small intestine into the enterocyte via either simple diffusion or trans-phosphorylation to thiamine monophosphate (TMP) but the majority occurs through active transport [1]. This active transport involves a carrier-mediated process that is believed to involve the human thiamine transporters hTHTR-1 and hTHTR-2. It is subsequently phosphorylated to thiamine diphosphate, the most abundant compound in the body, an essential coenzyme for the transketolase enzyme and the dehydrogenase complexes for pyruvate, alpha-ketoglutarate and branched-chain keto acids. All of these enzymes are essential in carbohydrate metabolism.

Thiamine is excreted through the kidneys, where hTHTR-1 and hTHTR-2 are involved in the re-uptake of thiamine in the proximal tubules. These are adaptively up-regulated in thiamine deficiency via transcriptional regulatory mechanisms, and thus the kidneys are responsible for thiamine homeostasis [2]. The thiamine transporters are also necessary for the uptake and regulation of thiamine in the pancreas where it essential for its normal endocrine function [3].

Thiamine status can be assessed directly by measuring thiamine levels in blood or urinary excretion before and after loading [4]. Alternatively a functional measure of thiamine status, erythrocyte transketolase activity can be measured, but this is influenced by many other factors other than thiamine deficiency, is relatively unstable on sampling and there is a lack of agreement over the upper limit of the reference range [5]. Microbiological assays measure red cell thiamine concentration but are

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3 time consuming and the sensitivity of the assays is not always sufficient for analyses  
4 of human body fluids [6]. The majority of the total thiamine content of whole blood  
5 is found in erythrocytes as TDP and has been shown to be a good indicator of body  
6 stores as it depletes at a rate similar to those of major organs. High performance  
7 liquid chromatography (HPLC) measurement of blood TDP levels has been  
8 determined to be a simple and precise way of assessing thiamine status [7].  
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## 11 ***Thiamine deficiency***

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14 Deficiency can occur as a result of inadequate intake, increased requirements (fever,  
15 pregnancy, breast feeding), excessive renal loss, consumption of anti-thiamine factors  
16 (tea, coffee, raw shellfish), or a combination of these factors. Severe deficiency results  
17 in beri-beri, which is termed, wet, dry, or cerebral (commonly known as Wernicke's  
18 Encephalopathy) depending on the system affected. In the western world Wernicke's  
19 Encephalopathy is most commonly associated with chronic alcoholism as a result of  
20 both a nutritional and absorptive deficiency.  
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24 Studies into Wernicke's Encephalopathy have shown the neuro-degeneration that  
25 occurs is strongly associated with increased endothelial nitric oxide synthase (eNOS)  
26 production, inter-cellular adhesion molecule 1 (ICAM-1) levels and the production of  
27 reactive oxygen species. It is not currently clear whether eNOS production induces  
28 neuronal damage through peroxynitrite formation or has a neuroprotective role in  
29 response to local inflammation [8]. There has also been shown to be a breakdown in  
30 the blood-brain barrier as a result of endothelial dysfunction, and decreased cerebral  
31 energy due to impaired glucose metabolism, which occurs as a result of decreased  
32 activity of  $\alpha$ -ketoglutarate dehydrogenase. Finally increased pro-inflammatory  
33 cytokines have been demonstrated in the thiamine deficient brain [9]. All of these  
34 pathological processes seen in the thiamine deficient brain are strongly associated  
35 with pathophysiology of insulin resistance and macrovascular disease [10, 11].  
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39 A Cochrane review has demonstrated a lack of evidence as to the dose, frequency,  
40 route or duration of thiamine treatment for prophylaxis against or treatment of  
41 Wernicke's Encephalopathy in people at risk from alcohol abuse[12]. However the  
42 Royal College of Physicians published guidelines advising treatment of at risk  
43 patients with high-dose parenteral thiamine to prevent the mortality associated with  
44 Wernicke's Encephalopathy and the development of Korsakoff's Psychosis[13].  
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## 47 ***Thiamine deficiency and diabetes mellitus – evidence, 48 mechanisms and replacement***

### 49 **Evidence**

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52 Several studies have demonstrated thiamine deficiency in individuals with both type 1  
53 and type 2 diabetes. Studies have shown altered erythrocyte transketolase activity  
54 indicating a risk of thiamine deficiency in both type 1 and type 2 diabetes, but the  
55 proportion of affected individuals varies from 17% to 79% across the studies [14-16].  
56 In addition, when comparing people with diabetes with the normal population, there  
57 was found to be no significant difference between erythrocyte transketolase activity  
58 levels in one study [17] but levels indicating a significantly higher risk of thiamine  
59 deficiency in another study [14].  
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3 Measurement of thiamine levels and its esters in blood, serum and plasma also reveals  
4 differing results across the studies. Three studies have shown reduced plasma  
5 thiamine concentrations in patients with diabetes [15, 17, 18], however red cell  
6 thiamine levels were low in 15% of patients with diabetes in one study [19] but  
7 normal in another [17].  
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10 The reasons for these differing results are not well understood. While some may be  
11 down to sampling and assay problems as described previously, not all the studies  
12 comment on the alcohol intake in the individuals or other potential causes of thiamine  
13 deficiency. Only the Jermendy and Thornalley papers [14, 17] specifically sited  
14 excess alcohol intake as an exclusion criteria, but direct comparison of these two  
15 papers reveal opposing results in erythrocyte transketolase activity as described  
16 above. In summary, whilst there is evidence of thiamine deficiency in individuals  
17 with diabetes, the prevalence is not known and further studies should be undertaken to  
18 determine this.  
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### 22 Mechanisms

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24 The reason for this deficiency is not well understood but several mechanisms may be  
25 responsible. Insulin deficiency is associated with a reduction in the rate of thiamine  
26 transport across the intestine and insulin deficient rats have been shown to have a net  
27 reduction in the transport of free thiamine and TMP but with a corresponding increase  
28 in TDP levels [20]. Conversely thiamine deficiency leads to a marked impairment in  
29 insulin synthesis and secretion [3] thereby insulin deficiency may exacerbate thiamine  
30 deficiency and vice-versa.  
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34 Thornalley showed that in the thiamine deficient state there is increased renal  
35 clearance and fractional excretion of thiamine and it has been hypothesised that this is  
36 secondary to decreased re-uptake of thiamine in renal proximal tubules, possibly an  
37 early marker of renal proximal tubule dysfunction in diabetes [17]. However a further  
38 study has shown increased plasma thiamine levels with progressive renal impairment  
39 and proteinuria suggesting decreased renal clearance of thiamine [21]. The reason for  
40 these differing results remains unclear and may be due to changes in the number  
41 and/or function of thiamine transporter proteins or due to increased or reduced  
42 filtration. Altered functioning of thiamine transporter proteins could, in theory, affect  
43 the hTHTR-1 and 2 proteins in both the gut and pancreas, with a reduction in active  
44 thiamine absorption and reduced pancreatic endocrine function, thus exacerbating  
45 both thiamine deficiency and hyperglycaemia.  
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### 50 Replacement

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52 Thiamine supplementation (>4mg per day) has been shown to normalise red cell  
53 thiamine levels in patients with diabetes, whereas increasing dietary thiamine intake  
54 above the recommended dietary intake of 1 to 1.4mg/day have not – suggesting a need  
55 for higher than normal thiamine intake in patients with diabetes compared with  
56 normal individuals [19]. Oral thiamine replacement is widely available in the UK as  
57 thiamine hydrochloride, a water soluble compound. Benfotiamine is a lipid-soluble  
58 allthiamine derivative that has better intestinal absorption and improved  
59 bioavailability but it is not currently available for prescription in the UK [22]. In one  
60 study five patients, who were treated with benfotiamine for seven days, showed a



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3 significant improvement in erythrocyte transketolase activity. This suggests an  
4 improvement in thiamine status [14], however this is a very small study and further  
5 work is necessary in this area,  
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## 10 ***Thiamine and hyperglycaemia – mechanisms of damage***

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13 Thiamine diphosphate is essential for carbohydrate metabolism. In the thiamine  
14 deficient state glucose undergoes metabolism via alternate pathways which can result  
15 in vascular damage. These pathways are summarised in figure 2.  
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18 Figure 2: Diagram detailing pathways of glucose metabolism. Thiamine diphosphate is an essential  
19 cofactor for the enzymes depicted in *italics*. Inhibition of these enzymes results in increased  
20 superoxide production ( $O_2^-$ ) and reduced flux through the pentose phosphate pathway with subsequent  
21 increased flux through the alternative pathways of glucose metabolism[23].  
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23 Adapted from Brownlee 2001 [23] and Hammes 2003 [24]  
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26 Several studies have been undertaken looking at the effect of thiamine and  
27 benfotiamine administration on these biochemical pathways. Animal studies have  
28 shown that high dose thiamine reduces activity through the hexosamine pathway [25].  
29 Thiamine supplementation can prevent hyperglycaemia driven reductions in cell  
30 replication and proliferation as well as decreasing AGE formation and reducing  
31 lactate levels [26]. In vitro studies with benfotiamine and thiamine have shown a  
32 reduction in protein kinase C activation in the glomeruli and decreased glomerular  
33 AGE levels [27]. Benfotiamine has been shown to prevent increased markers of  
34 hexosamine pathway activity, intracellular AGE formation, intracellular protein  
35 kinase C activity and NF- $\kappa$ B activation seen with in vitro hyperglycaemic damage  
36 [24]. Oral benfotiamine in combination with the anti-oxidant  $\alpha$ -lipoic acid treatment  
37 normalises production of angiotensin-2, a marker of increased intracellular  
38 methylglyoxals in endothelial cells which contribute to AGE formation, and N-  
39 acetylglucose modified protein, a marker of hexosamine pathway activity [28]. Both  
40 thiamine and benfotiamine have been shown to reduce AGE formation in  
41 experimental diabetes [29]. Treatment with both thiamine and benfotiamine has been  
42 shown to reduce activation of the polyol pathway of glucose metabolism and to  
43 increase transketolase expression in the presence of hyperglycaemia [30].  
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49 Collectively this data suggests that administration of thiamine or a derivative can  
50 influence carbohydrate metabolism by reducing metabolism through the alternate  
51 pathways of metabolism and improving metabolism via the pentose-phosphate  
52 pathway. This has been demonstrated in diabetic animal models where treatment with  
53 thiamine reduced fasting glucose and HbA1c levels [31] and also in humans with type  
54 2 diabetes, where a short duration of treatment with thiamine (150mg per day for 1  
55 month) showed a significant improvement in fasting glucose levels [32].  
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## Thiamine, endothelial function and oxidative stress

Multiple studies have looked at the effect of thiamine upon endothelial function and oxidative stress and several are summarised in table 1.

Study	Mode	Salient points
Lukienko '00 <sup>[33]</sup>	<i>In vitro</i> (rat liver cells)	Thiamine inhibits lipid peroxidation and oxidation of oleic acid
Ascher '01 <sup>[34]</sup>	<i>In vitro</i> (bovine)	Thiamine inhibited hyperglycaemia driven endothelial cell activation and prevented the effects of hyperglycaemia on endothelial cell migration
Arora '06 <sup>[35]</sup>	<i>In vivo</i> (humans)	Iv thiamine improved endothelium dependant vasodilatation in presence of hyperglycaemia
Stirban et al '06 <sup>[36]</sup>	<i>In vivo</i> (humans)	BT prevented macro and micro vascular endothelial dysfunction
Thornalley '07 <sup>[17]</sup>	<i>In vivo</i> (humans)	Negative correlation between plasma thiamine levels and VCAM-1
Wong '07 <sup>[37]</sup>	<i>In vivo</i> (humans)	Increased dietary thiamine intake associated with increased no of endothelial progenitor cells and improved vascular endothelial function
Balakumar '08 <sup>[38]</sup>	<i>In vivo</i> (rats)	Benfotiamine prevented vascular endothelial dysfunction and oxidation stress.
Schmid et al '08 <sup>[39]</sup>	<i>In vitro</i> (human, rat and porcine kidney cells)	Benfotiamine prevents oxidative stress
Schupp '08 <sup>[40]</sup>	<i>In vivo</i> (humans)	Benfotiamine increased antioxidant capacity of plasma in dialysis patients.
Balakumar '09 <sup>[41]</sup>	<i>In vivo</i> (rats)	Benfotiamine reduces the oxidative stress and enhances the generation of nitric oxide to prevent VED.
Verma '09 <sup>[42]</sup>	<i>In vivo</i> (rats)	Benfotiamine prevented induced oxidative stress

Table 1: Studies examining the effect of thiamine and benfotiamine on endothelial function and oxidative stress.

VCAM-1 = vascular cellular adhesion molecule; VED = vascular endothelial dysfunction

The antioxidant properties of thiamine have been known since the 1950's. This has been shown in foodstuffs where rye bread, containing a higher content of thiamine than wheat dough, has a higher antioxidant activity [43]. In 2000, Lukienko et al demonstrated that thiamine inhibited lipid peroxidation in vitro and Schmid et al demonstrated the antioxidant properties of benfotiamine in kidney cell lines [39]. In vivo animal studies have shown benfotiamine can reduce oxidative stress when induced either through chemical means (sodium arsenite, nicotine or uric-acid) or diabetes [38, 41, 42]. The anti-oxidative capacity of benfotiamine has also been demonstrated in patients with diabetes and those undergoing dialysis [36, 40].

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Improved endothelial function in a thiamine-rich environment has been demonstrated by a reversal of hyperglycaemia induced reduction in endothelial cell migration and proliferation. In addition increased von Willibrand factor levels, a marker of endothelial cell damage, are reduced when wounded endothelial cells are treated with thiamine [34]. Animal models have shown benfotiamine reduces oxidative stress and activates endothelial nitric oxide synthase to enhance the generation and bioavailability of NO, subsequently improving the integrity of vascular endothelium and preventing induced experimental vascular endothelial dysfunction (VED) [41, 42]. In individuals with diabetes there is a negative correlation between plasma thiamine levels and endothelial dysfunction [17, 37] and endothelial dysfunction is prevented by both benfotiamine and thiamine [35, 36].

This strong body of evidence demonstrates thiamine or its derivatives act as antioxidants and have a beneficial effect on endothelial function. These changes are seen in both the euglycaemic and hyperglycaemic environment.

### ***Thiamine and vascular disease***

Microalbuminuria, an early indicator of diabetic nephropathy, is associated with an increased cardiovascular risk in individuals with and without diabetes [44]. In vitro studies with benfotiamine and thiamine have shown the ability to prevent microalbuminuria and proteinuria in diabetic rats. In vivo studies have shown that high dose oral supplementation with thiamine compared with placebo significantly reduces urinary albumin excretion in individuals [45, 46]. However reduction in microalbuminuria, with benfotiamine, was not evident in patients already receiving angiotensin converting enzyme inhibitors or angiotensin II receptor blockers [47].

Thiamine has been shown to prevent apoptosis of human retinal pericytes, loss of which represents an early stage in the development of diabetic retinopathy [48]. In vivo studies have also shown benfotiamine treatment prevented the development of experimental diabetic retinopathy in rats [24].

Thiamine has been demonstrated to have significant analgesic effects in neuropathic pain. In addition it has shown beneficial acute and chronic anti-inflammatory actions upon induced skin lesions [49]. Further studies in diabetic neuropathy have shown a beneficial effect of benfotiamine upon several modalities of neuropathic pain [50] and another study in humans suggested benfotiamine improved pain in diabetic polyneuropathy [51].

Animal studies have shown that high dose thiamine, but not benfotiamine, therapy prevented diabetes-associated dyslipidaemia [25].

## Conclusions

It is well known that glucose metabolism is dependent upon thiamine as a cofactor and in the hyperglycaemic environment alternative pathways of metabolism (that are not thiamine dependant) are activated. This leads to increased formation of harmful by-products which contribute to the pathophysiology of diabetic complications. In addition thiamine has direct action on the endocrine function of the pancreas and, therefore, deficiency may contribute to hyperglycaemia through other mechanisms rather than impaired glucose metabolism.

Thiamine and its derivatives have been shown to improve endothelial function and reduce oxidative stress in both the normo- and hyperglycaemic environment. Given that these processes are closely linked with vascular inflammation it could be hypothesised that thiamine has anti-inflammatory properties. There is some evidence that this is seen in induced skin inflammation but vascular inflammation has not been extensively studied.

It has been demonstrated that thiamine has a beneficial effect upon several features of the metabolic syndrome such as microalbuminuria, a surrogate marker of vascular risk, and glycaemic control, and it could be hypothesised that thiamine supplementation may have beneficial effects upon integrally linked pathophysiological processes such as insulin resistance and hypertension.

All of the above processes are involved in the development of vascular complications in diabetes but it is not clear is whether thiamine therapy may have beneficial clinical effects in individuals with diabetes, through reducing cardiovascular risk and microvascular complications. It also remains to be determined whether any benefit that occurs is as a result of replacing thiamine in individuals who are prone to deficiency or by saturation and promotion of thiamine dependent pathways leading to an improvement in endothelial function and/or oxidative stress. All of these areas warrant further investigation.

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4 **Author Contributions**

5 Dr G Page: acquisition of papers, data interpretation, drafting article

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7  
8 Dr D Laight: acquisition of papers, critical revision of article, approval of article

9  
10 Prof M H Cummings: article concept design, critical revision of article, approval of  
11 article  
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## References

- [1] Rindi G, Laforenza U. Thiamine intestinal transport and related issues: recent aspects. *Proceedings of the Society for Experimental Biology and Medicine Society for Experimental Biology and Medicine* (New York, NY. 2000 Sep;224(4):246-55.
- [2] Ashokkumar B, Vaziri ND, Said HM. Thiamin uptake by the human-derived renal epithelial (HEK-293) cells: cellular and molecular mechanisms. *Am J Physiol Renal Physiol*. 2006 Oct;291(4):F796-805.
- [3] Mee L NS, Sekar VT, Subramanian VS, Maedler K, Said HM. Pancreatic beta cells and islets take up thiamin by a regulated carrier-mediated process: studies using mice and human pancreatic preparations. *Am J Physiol Gastrointest Liver Physiol*. 2009;297:G197-G206.
- [4] Food Standards Agency U. Expert Group on Vitamins and Minerals. 74 - 80.
- [5] Talwar D, Davidson H, Cooney J, St JRD. Vitamin B(1) status assessed by direct measurement of thiamin pyrophosphate in erythrocytes or whole blood by HPLC: comparison with erythrocyte transketolase activation assay. *Clinical chemistry*. 2000 May;46(5):704-10.
- [6] Tallaksen CM, Bohmer T, Karlsen J, Bell H. Determination of thiamin and its phosphate esters in human blood, plasma, and urine. *Methods in enzymology*. 1997;279:67-74.
- [7] Lu J, Frank EL. Rapid HPLC measurement of thiamine and its phosphate esters in whole blood. *Clinical chemistry*. 2008 May;54(5):901-6.
- [8] De Palma C, Falcone S, Panzeri C, Radice S, Bassi MT, Clementi E. Endothelial nitric oxide synthase overexpression by neuronal cells in neurodegeneration: a link between inflammation and neuroprotection. *Journal of neurochemistry*. 2008 Jul;106(1):193-204.
- [9] Hazell AS, Butterworth RF. Update of cell damage mechanisms in thiamine deficiency: focus on oxidative stress, excitotoxicity and inflammation. *Alcohol and alcoholism (Oxford, Oxfordshire)*. 2009 Mar-Apr;44(2):141-7.
- [10] Stehouwer CD, Schaper NC. The pathogenesis of vascular complications of diabetes mellitus: one voice or many? *European journal of clinical investigation*. 1996 Jul;26(7):535-43.
- [11] Hartge MM, Kintscher U, Unger T. Endothelial dysfunction and its role in diabetic vascular disease. *Endocrinology and metabolism clinics of North America*. 2006 Sep;35(3):551-60, viii-ix.
- [12] Day E, Bentham P, Callaghan R, Kuruvilla T, George S. Thiamine for Wernicke-Korsakoff Syndrome in people at risk from alcohol abuse. *Cochrane database of systematic reviews (Online)*. 2004(1):CD004033.
- [13] Thomson AD, Cook CC, Touquet R, Henry JA. The Royal College of Physicians report on alcohol: guidelines for managing Wernicke's encephalopathy in the accident and Emergency Department. *Alcohol and alcoholism (Oxford, Oxfordshire)*. 2002 Nov-Dec;37(6):513-21.
- [14] Jermendy G. Evaluating thiamine deficiency in patients with diabetes. *Diab Vasc Dis Res*. 2006 Sep;3(2):120-1.
- [15] Saito N, Kimura M, Kuchiba A, Itokawa Y. Blood thiamine levels in outpatients with diabetes mellitus. *Journal of nutritional science and vitaminology*. 1987 Dec;33(6):421-30.
- [16] Lemoine A, Le Devehat C, Codaccioni JL, Monges A, Bermond P, Salkeld RM. Vitamin B1, B2, B6, and C status in hospital inpatients. *The American journal of clinical nutrition*. 1980 Dec;33(12):2595-600.

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3  
4 [17] Thornalley PJ, Babaei-Jadidi R, Al Ali H, Rabbani N, Antonysunil A, Larkin  
5 J, et al. High prevalence of low plasma thiamine concentration in diabetes linked to a  
6 marker of vascular disease. *Diabetologia*. 2007 Oct;50(10):2164-70.
- 7 [18] Valerio G, Franzese A, Poggi V, Patrini C, Laforenza U, Tenore A. Lipophilic  
8 thiamine treatment in long-standing insulin-dependent diabetes mellitus. *Acta*  
9 *diabetologica*. 1999 Jun;36(1-2):73-6.
- 10 [19] Vindedzis SA, Stanton KG, Sherriff JL, Dhaliwal SS. Thiamine deficiency in  
11 diabetes - is diet relevant? *Diab Vasc Dis Res*. 2008 Sep;5(3):215.
- 12 [20] Patrini C LU, Gastaldi G, Verri A, Ferrari G, Rindi G. Effect of insulin on  
13 thiamine intestinal transport in rat everted jejunal sacs. *Journal of Physiology*.  
14 1996;493:100S-1S.
- 15 [21] Pacal L, Tomandl J, Svojanovsky J, Krusova D, Stepankova S, Rehorova J, et  
16 al. Role of thiamine status and genetic variability in transketolase and other pentose  
17 phosphate cycle enzymes in the progression of diabetic nephropathy. *Nephrol Dial*  
18 *Transplant*. Sep 8.
- 19 [22] Schreeb KH, Freudenthaler S, Vormfelde SV, Gundert-Remy U, Gleiter CH.  
20 Comparative bioavailability of two vitamin B1 preparations: benfotiamine and  
21 thiamine mononitrate. *European journal of clinical pharmacology*. 1997;52(4):319-20.
- 22 [23] Brownlee M. Biochemistry and molecular cell biology of diabetic  
23 complications. *Nature*. 2001 Dec 13;414(6865):813-20.
- 24 [24] Hammes HP, Du X, Edelstein D, Taguchi T, Matsumura T, Ju Q, et al.  
25 Benfotiamine blocks three major pathways of hyperglycemic damage and prevents  
26 experimental diabetic retinopathy. *Nature medicine*. 2003 Mar;9(3):294-9.
- 27 [25] Babaei-Jadidi R, Karachalias N, Kupich C, Ahmed N, Thornalley PJ. High-  
28 dose thiamine therapy counters dyslipidaemia in streptozotocin-induced diabetic rats.  
29 *Diabetologia*. 2004 Dec;47(12):2235-46.
- 30 [26] La Selva M, Beltramo E, Pagnozzi F, Bena E, Molinatti PA, Molinatti GM, et  
31 al. Thiamine corrects delayed replication and decreases production of lactate and  
32 advanced glycation end-products in bovine retinal and human umbilical vein  
33 endothelial cells cultured under high glucose conditions. *Diabetologia*. 1996  
34 Nov;39(11):1263-8.
- 35 [27] Babaei-Jadidi R, Karachalias N, Ahmed N, Battah S, Thornalley PJ.  
36 Prevention of incipient diabetic nephropathy by high-dose thiamine and benfotiamine.  
37 *Diabetes*. 2003 Aug;52(8):2110-20.
- 38 [28] Du X, Edelstein D, Brownlee M. Oral benfotiamine plus alpha-lipoic acid  
39 normalises complication-causing pathways in type 1 diabetes. *Diabetologia*. 2008  
40 Oct;51(10):1930-2.
- 41 [29] Karachalias N, Babaei-Jadidi R, Rabbani N, Thornalley PJ. Increased protein  
42 damage in renal glomeruli, retina, nerve, plasma and urine and its prevention by  
43 thiamine and benfotiamine therapy in a rat model of diabetes. *Diabetologia*. 2010  
44 Jul;53(7):1506-16.
- 45 [30] Berrone E, Beltramo E, Solimine C, Ape AU, Porta M. Regulation of  
46 intracellular glucose and polyol pathway by thiamine and benfotiamine in vascular  
47 cells cultured in high glucose. *The Journal of biological chemistry*. 2006 Apr  
48 7;281(14):9307-13.
- 49 [31] Thornalley PJ B-JR, Karachalias N, Rabbani N. Prevention of decline in  
50 glycaemic control in streptozocin-induced diabetic rats by thiamine but not by  
51 Benfotiamine. *Diabet Med*. 2010 March 2010;27(Supplement 1):74.
- 52 [32] Gonzalez-Ortiz M, Martinez-Abundis E, Robles-Cervantes JA, Ramirez-  
53 Ramirez V, Ramos-Zavala MG. Effect of thiamine administration on metabolic  
54  
55  
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57  
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2  
3 profile, cytokines and inflammatory markers in drug-naive patients with type 2  
4 diabetes. *European journal of nutrition*. Jul 21.
- 5  
6 [33] Lukienko PI, Mel'nichenko NG, Zverinskii IV, Zabrodskaia SV. Antioxidant  
7 properties of thiamine. *Bulletin of experimental biology and medicine*. 2000  
8 Sep;130(9):874-6.
- 9  
10 [34] Ascher E, Gade PV, Hingorani A, Puthukkeril S, Kallakuri S, Scheinman M,  
11 et al. Thiamine reverses hyperglycemia-induced dysfunction in cultured endothelial  
12 cells. *Surgery*. 2001 Nov;130(5):851-8.
- 13  
14 [35] Arora S, Lidor A, Abularrage CJ, Weiswasser JM, Nylén E, Kellicut D, et al.  
15 Thiamine (vitamin B1) improves endothelium-dependent vasodilatation in the  
16 presence of hyperglycemia. *Annals of vascular surgery*. 2006 Sep;20(5):653-8.
- 17  
18 [36] Stirban A, Negrean M, Stratmann B, Gawlowski T, Horstmann T, Gotting C,  
19 et al. Benfotiamine prevents macro- and microvascular endothelial dysfunction and  
20 oxidative stress following a meal rich in advanced glycation end products in  
21 individuals with type 2 diabetes. *Diabetes care*. 2006 Sep;29(9):2064-71.
- 22  
23 [37] Wong CY, Qiuwaxi J, Chen H, Li SW, Chan HT, Tam S, et al. Daily intake of  
24 thiamine correlates with the circulating level of endothelial progenitor cells and the  
25 endothelial function in patients with type II diabetes. *Molecular nutrition & food  
26 research*. 2008 Dec;52(12):1421-7.
- 27  
28 [38] Balakumar P, Sharma R, Singh M. Benfotiamine attenuates nicotine and uric  
29 acid-induced vascular endothelial dysfunction in the rat. *Pharmacol Res*. 2008 Nov-  
30 Dec;58(5-6):356-63.
- 31  
32 [39] Schmid U, Stopper H, Heidland A, Schupp N. Benfotiamine exhibits direct  
33 antioxidative capacity and prevents induction of DNA damage in vitro.  
34 *Diabetes/metabolism research and reviews*. 2008 Jul-Aug;24(5):371-7.
- 35  
36 [40] Schupp N, Dette EM, Schmid U, Bahner U, Winkler M, Heidland A, et al.  
37 Benfotiamine reduces genomic damage in peripheral lymphocytes of hemodialysis  
38 patients. *Naunyn-Schmiedeberg's archives of pharmacology*. 2008 Sep;378(3):283-91.
- 39  
40 [41] Balakumar P, Chakkarwar VA, Singh M. Ameliorative effect of combination  
41 of benfotiamine and fenofibrate in diabetes-induced vascular endothelial dysfunction  
42 and nephropathy in the rat. *Molecular and cellular biochemistry*. 2009 Jan;320(1-  
43 2):149-62.
- 44  
45 [42] Verma S, Reddy K, Balakumar P. The defensive effect of benfotiamine in  
46 sodium arsenite-induced experimental vascular endothelial dysfunction. *Biological  
47 trace element research*. Oct;137(1):96-109.
- 48  
49 [43] Martinez-Villaluenga C, Michalska A, Frias J, Piskula MK, Vidal-Valverde C,  
50 Zielinski H. Effect of flour extraction rate and baking on thiamine and riboflavin  
51 content and antioxidant capacity of traditional rye bread. *Journal of food science*.  
52 2009 Jan-Feb;74(1):C49-55.
- 53  
54 [44] Stehouwer CD, Smulders YM. Microalbuminuria and risk for cardiovascular  
55 disease: Analysis of potential mechanisms. *J Am Soc Nephrol*. 2006 Aug;17(8):2106-  
56 11.
- 57  
58 [45] Rabbani N, Alam SS, Riaz S, Larkin JR, Akhtar MW, Shafi T, et al. High-  
59 dose thiamine therapy for patients with type 2 diabetes and microalbuminuria: a  
60 randomised, double-blind placebo-controlled pilot study. *Diabetologia*. 2009  
Feb;52(2):208-12.
- [46] Riaz S, Skinner V, Srail SK. Effect of high dose thiamine on the levels of  
urinary protein biomarkers in diabetes mellitus type 2. *Journal of pharmaceutical and  
biomedical analysis*. Mar 25;54(4):817-25.



- 1  
2  
3 [47] Alkhalaf A KA, et al. A double-blind, randomized, placebo-controlled clinical  
4 trial on benfotiamine treatment in patients with diabetic nephropathy. *Diabetes care*.  
5 2010.  
6  
7 [48] Beltramo E, Nizheradze K, Berrone E, Tarallo S, Porta M. Thiamine and  
8 benfotiamine prevent apoptosis induced by high glucose-conditioned extracellular  
9 matrix in human retinal pericytes. *Diabetes/metabolism research and reviews*. 2009  
10 Oct;25(7):647-56.  
11 [49] Moallem SA, Hosseinzadeh H, Farahi S. A study of acute and chronic anti-  
12 nociceptive and anti-inflammatory effects of thiamine in mice. *Iranian biomedical*  
13 *journal*. 2008 Jul;12(3):173-8.  
14 [50] Sanchez-Ramirez GM, Caram-Salas NL, Rocha-Gonzalez HI, Vidal-Cantu  
15 GC, Medina-Santillan R, Reyes-Garcia G, et al. Benfotiamine relieves inflammatory  
16 and neuropathic pain in rats. *European journal of pharmacology*. 2006 Jan 13;530(1-  
17 2):48-53.  
18 [51] Stracke H, Gaus W, Achenbach U, Federlin K, Bretzel RG. Benfotiamine in  
19 diabetic polyneuropathy (BENDIP): results of a randomised, double blind, placebo-  
20 controlled clinical study. *Exp Clin Endocrinol Diabetes*. 2008 Nov;116(10):600-5.  
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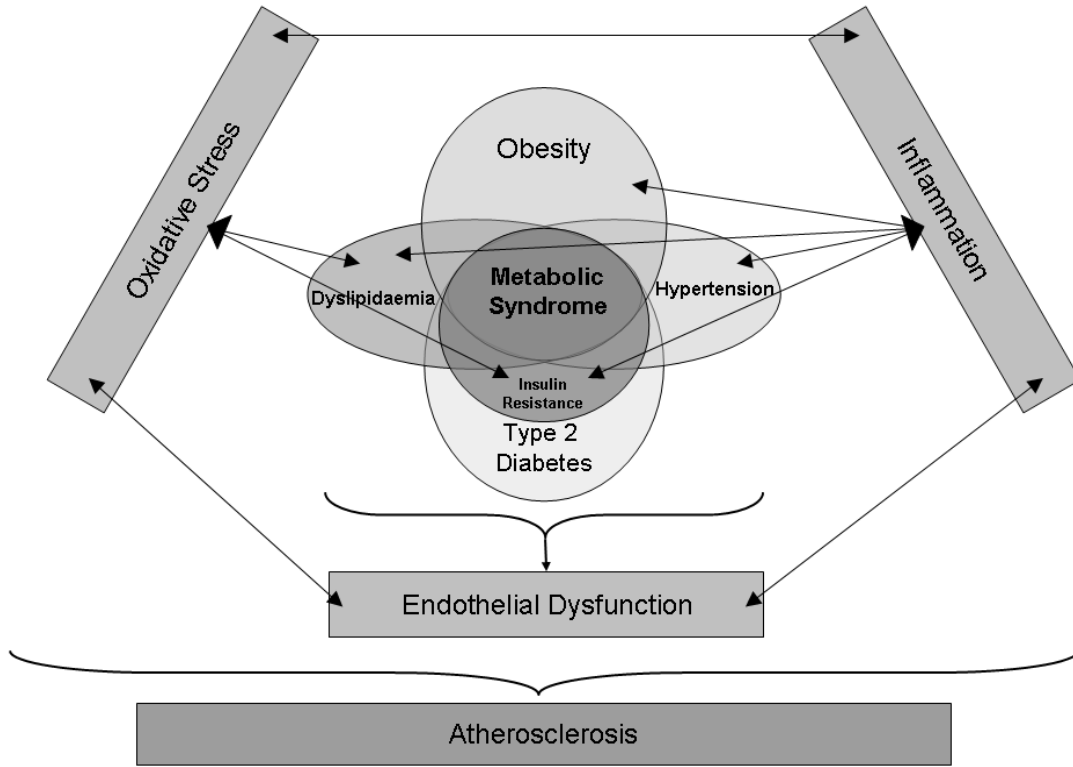


Figure 1: Diagram showing the relationship between the metabolic syndrome and its components to oxidative stress, inflammation and endothelial dysfunction. All these processes contribute to atherosclerosis.

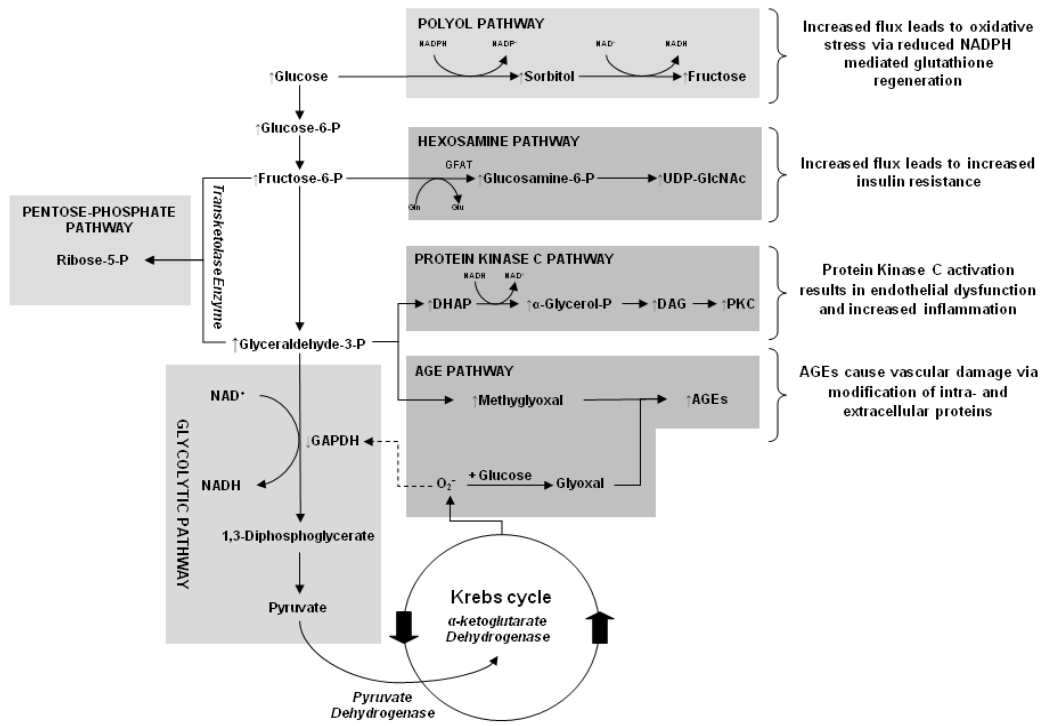


Figure 2

Review Only