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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 α -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, mechanisms and replacement***

48 **Evidence**

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51 Several studies have demonstrated thiamine deficiency in individuals with both type 1
52 and type 2 diabetes. Studies have shown altered erythrocyte transketolase activity
53 indicating a risk of thiamine deficiency in both type 1 and type 2 diabetes, but the
54 proportion of affected individuals varies from 17% to 79% across the studies [14-16].
55 In addition, when comparing people with diabetes with the normal population, there
56 was found to be no significant difference between erythrocyte transketolase activity
57 levels in one study [17] but levels indicating a significantly higher risk of thiamine
58 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].
22

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- κ B activation seen with in vitro hyperglycaemic damage
36 [24]. Oral benfotiamine in combination with the anti-oxidant α -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 ^[33]	<i>In vitro</i> (rat liver cells)	Thiamine inhibits lipid peroxidation and oxidation of oleic acid
Ascher '01 ^[34]	<i>In vitro</i> (bovine)	Thiamine inhibited hyperglycaemia driven endothelial cell activation and prevented the effects of hyperglycaemia on endothelial cell migration
Arora '06 ^[35]	<i>In vivo</i> (humans)	Iv thiamine improved endothelium dependant vasodilatation in presence of hyperglycaemia
Stirban et al '06 ^[36]	<i>In vivo</i> (humans)	BT prevented macro and micro vascular endothelial dysfunction
Thornalley '07 ^[17]	<i>In vivo</i> (humans)	Negative correlation between plasma thiamine levels and VCAM-1
Wong '07 ^[37]	<i>In vivo</i> (humans)	Increased dietary thiamine intake associated with increased no of endothelial progenitor cells and improved vascular endothelial function
Balakumar '08 ^[38]	<i>In vivo</i> (rats)	Benfotiamine prevented vascular endothelial dysfunction and oxidation stress.
Schmid et al '08 ^[39]	<i>In vitro</i> (human, rat and porcine kidney cells)	Benfotiamine prevents oxidative stress
Schupp '08 ^[40]	<i>In vivo</i> (humans)	Benfotiamine increased antioxidant capacity of plasma in dialysis patients.
Balakumar '09 ^[41]	<i>In vivo</i> (rats)	Benfotiamine reduces the oxidative stress and enhances the generation of nitric oxide to prevent VED.
Verma '09 ^[42]	<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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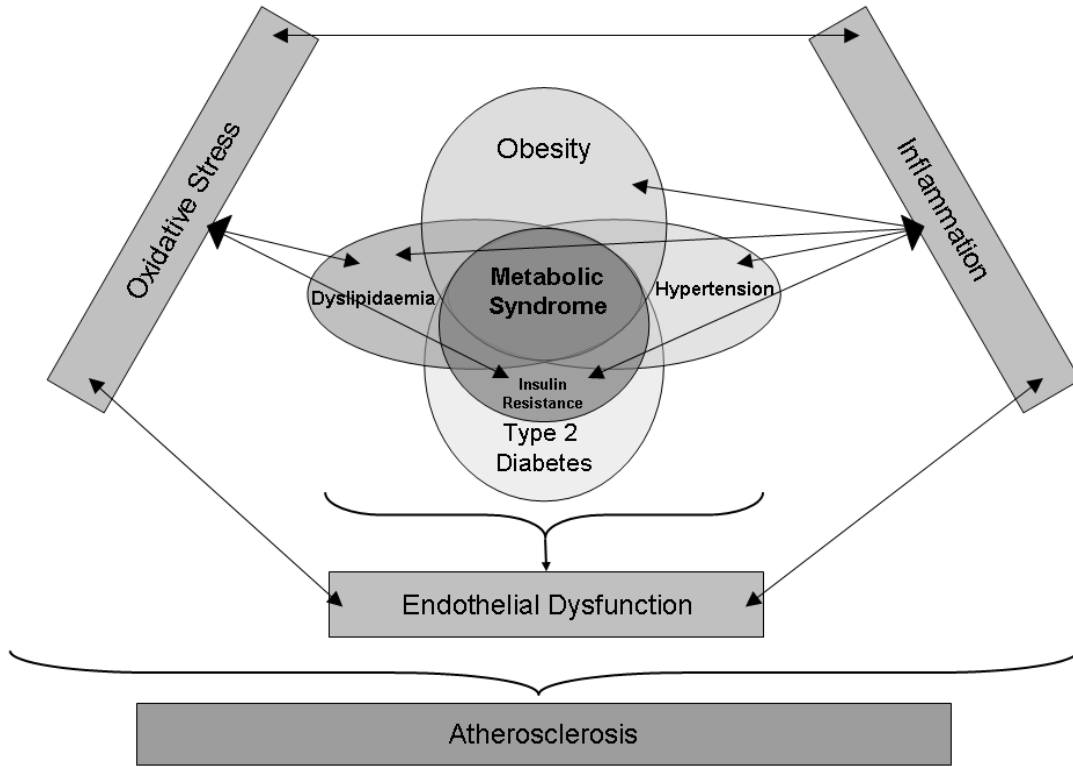


Figure 1: Diagram showing the relationship between the metabolic syndrome and its components to oxidative stress, inflammation and endothelial dysfunction. All these processes contribute to atherosclerosis.

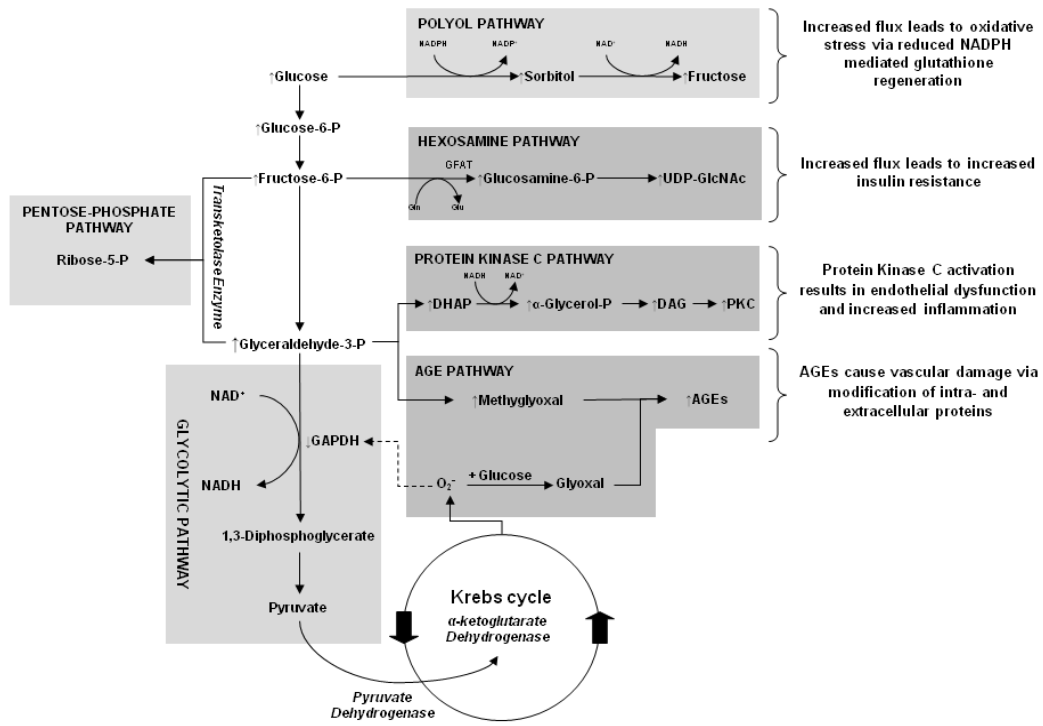


Figure 2

Review Only