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Editorial

Vitamin B_6 (pyridoxamine) supplementation and complications of diabetes☆

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Pyridoxine is known to be rapidly taken up by the red blood cells and converted to pyridoxamine and pyridoxal phosphate, which serve as the coenzyme for the transaminases [1,2]. Pyridoxine, pyridoxamine, and pyridoxal phosphate form the vitamin B_6 group of compounds and are interconvertible within the cell. Vitamin B_6 (pyridoxine) is a catalytically inactive form, whereas pyridoxal (aldehyde form) and pyridoxamine (amine form) are catalytically active and are involved in a wide variety of both nonenzymatic and enzymatic reactions [1,2]. The vitamin B_6 group of compounds plays a major role in 1-carbon metabolism in the cell; for instance, PP is essential for the biosynthesis of the methyl group of methionine via the condensation of homocyteine and serine by the enzymes cystathionine β-synthase and cystathionine γ-lyase [3].

Early studies on development of atherosclerosis in monkeys fed with a vitamin B_6-deficient diet led to the idea that vitamin B_6 deficiency causes the development of vascular disease [4]. Studies in humans showed that plasma levels of vitamin B_6 were lower in subjects who had had myocardial infarction than in controls [5]. The Nurses Health Study, which included more than 80 000 women, also suggested a higher incidence of coronary artery disease in patients with lower levels of vitamin B_6 intake compared with those with higher intakes [6]. Several other studies also suggest that low blood vitamin B_6 concentrations are independently associated with a risk of coronary artery disease [7,8].

Blood vitamin B_6 levels are significantly decreased in experimental diabetic animals and diabetic patients [9-21]. Vitamin B_6 deficiency in animals is known to reduce pancreatic and circulating insulin levels [22]. Vitamin B_6 deficiency has been associated with degenerative changes in β-cells in the islets of Langerhans and abnormal glucose tolerance [23]. Pyridoxine supplementation restores normal glucose tolerance [24,25] and reduces the thickening of the glomerular basement membrane [21]. Long-term pyridoxine treatment to diabetic patients prevented retinopathy [9]. Supplementation of pyridoxine can lower blood glucose levels in streptozotocin-treated diabetic animals and glycosylated hemoglobin levels in type 2 diabetic patients [18,19]. In vitro studies have shown that pyridoxamine can inhibit formation of glycation end products [26-28]. Pyridoxal phosphate or pyridoxine has also been proposed to inhibit nonenzymatic glycosylation in diabetes [27]. Several studies found a significant reduction in neuropathy after vitamin B_6 supplementation to diabetic patients [15,17,19]. Thus, diabetes is associated with lower levels of vitamin B_6. On the other hand, vascular disease is a hallmark of the complications of diabetes. Can vitamin B_6 supplementation reduce the incidence of vascular disease in diabetes? If so, the biochemical mechanism by which vitamin B_6 supplementation may exert a beneficial effect against vascular disease in diabetes is not clear.

In this issue of Metabolism, Tanimoto and colleagues [29] demonstrate for the first time that supplementation with pyridoxamine (K-163) improves urinary albumin-to-creatinine ratios and serum 3-deoxyglucosone levels in KK-Ay/Ta mice, a spontaneous animal model for type 2 diabetic nephropathy. This is a novel observation. This finding potentially could be useful in the care and treatment of diabetic patients. Pyridoxamine is a post-Amadori inhibitor of advanced glycation endproduct (AGE) formation [26-28]. This study of Tanimoto and colleagues [29] also shows inhibition of markers of AGE, such as carboxymethyl lysine modified collagen (CML) and nitrotyrosine accumulation in the kidney tissue, as well as blood levels of hemoglobin A_{1c} in pyridoxamine-supplemented rats. The strength of this study is that the investigators demonstrate that not only

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pyridoxamine inhibits AGEs and markers of oxidative stress, but also an improvement in kidney function in this model of type 2 diabetes mellitus. Yet, there remain several unanswered questions, such as, what is the effect of pyridoxamine on the onset of diabetes in this model of diabetes? In this study, Tanimoto and colleagues [29] did not examine the effect of pyridoxamine on the complete blood count and liver functions. Complete blood count measurements are needed to rule out that the reduction in hemoglobin A_{1c} value reported in this study is not because of a reduction in red cell life span in pyridoxamine-supplemented rats.

Pyridoxamine has been shown to be a potent inhibitor of AGE formation [26-28]. Other investigators have also shown that pyridoxamine limited the progression of nephropathy, retinopathy, and dyslipidemia in streptozotocin-treated rats [30-33]. However, similar to the results from this study, previous studies also did not find any effect of pyridoxamine on glycemia. No studies have been performed that have examined whether pyridoxamine influences the insulin sensitivity or the development of diabetes in humans or in animal models of diabetes. For example, it would have been very interesting if the present study by Tanimoto and colleagues had examined whether pyridoxamine supplementation delays the onset of hyperglycemia in KK-Ay/Ta mice model. The cell culture studies [34] do suggest that pyridoxamine can restore altered mitochondrial membrane potential, one of the factors leading to insulin resistance in cells. Vitamin B_6 has the potential to delay diabetes-associated cataract formation [35-37]. The studies so far suggest that pyridoxamine may be inhibiting formation of AGE and trapping or scavenging the reactive oxygen species and its oxidation products caused/generated by hyperglycemia or ketonemia [33-38].

Diabetes is associated with hyperglycemia and hyperketonemia, both of which generate reactive oxygen species [39-43]. If this free radical is not readily neutralized by an antioxidant, it can go on to create more reactive free radicals, and cause damage to the cell membrane bilayer, vessel wall, proteins, lipids, and even the nucleic acids in the cell [44,45]. Many micronutrients such as selenium, trivalent chromium, zinc, manganese, tocotrienols, carotenoids, and vitamins E, C, and B_6 help maintain an effective antioxidative defense mechanism [44,45]. Most antioxidants are electron donors that react with free radicals to form innocuous end products such as water, thus protecting the cell against oxidative stress and damage [44,45]. Thus, diabetes is a state of imbalance between oxidant stress and antioxidative defense mechanisms that favors the former. Accumulation of oxygen radicals can peroxidize the lipid and protein structure of the membrane bilayer, inducing a variety of cellular dysfunctions that ultimately lead to tissue pathology. Biochemical pathways by which oxidative stress may cause cellular damage include changes in intracellular redox state, overexpression of multiple genes in vascular cells, and altered signal transduction pathways. The pathophysiology includes mitochondrial dysfunction, reduced nitrous oxide activities, damage to the endothelium lining of the arterial wall, increased monocyte and platelet adhesion, ischemia, apoptosis, increased procoagulant activity, and the degradation of fibrin. Overall, this increases the risk for vascular inflammation, increased formation of atherosclerotic plaques, thrombosis, and myocardial infarction [44].

There has been a significant interest in oxidative stress and its role in the development of complications in diabetic patients [39-48]. There appears to be increased requirement/utilization of vitamin B_6 in diabetes [49]. No previous studies have determined the effect of pyridoxamine supplementation on blood or tissue levels of oxidative stress in diabetic animals or patients. Pyridoxamine is also known to scavenge oxygen radicals as well as trap dicarbonyl intermediates during AGE formation [26-28,38], and has been shown to inhibit collagen cross-linking in a diabetic animal model [30]. Previous studies have reported an increase in lipid peroxidation levels in the plasma, kidney, heart, and liver and reduction in vitamin E and vitamin C levels in the plasma of rats fed a vitamin B_6–deficient diet [50]. These studies indicate that vitamin B_6 can act as an antioxidant, directly or indirectly. Whether modified pyridoxamine, such as adduct of pyridoxamine with aminoguanidine, is a better antioxidant and have better efficacy against the complications of diabetes is also under investigation [37,51].

The major strength of this article is that investigators determined both the biochemical markers of tissue injury such as AGEs in both blood and renal tissues, along with simultaneous normalization of renal pathology. Such data provide a mechanistic link to suggest a role of AGE and its inhibition by pyridoxamine in the development of nephropathy associated with diabetes. It is not yet clear what specific mechanisms are involved by which pyridoxamine plays a beneficial role in the prevention of vascular disease in diabetic patients.

In conclusion, various studies in the literature suggest that pyridoxamine or vitamin B_6 supplementation can be potentially beneficial and may prevent the development of nephropathy and vascular disease in diabetes. However, further long-term studies are needed in which both the parameters of liver functions, vascular inflammation, AGEs, and oxidative stress, as well as the development of renal, retinal, and vascular pathology, are examined both in type 1 and type 2 diabetic animal models.

The long-term complications of diabetes are the leading causes of morbidity and mortality in the diabetic population and remain a major public health issue. Eventually, many diabetic patients develop microvascular and macrovascular complications such as retinopathy, nephropathy, neuropathy, and accelerated atherosclerosis. Type 2 diabetes mellitus is treated with diet, exercise, and medication, and type 1 with diet and insulin administration. However, for many patients, achieving tight glucose control is difficult with current regimens. Given the enormous public health cost of

diabetes, further studies are needed to explore the potential use of a relatively low-cost dietary supplement, such as pyridoxamine or vitamin B_6, as an adjuvant therapy in the prevention of complications in diabetic patients.

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