Vitamin E Improves Microsomal Phospholipase A\textsubscript{2} Activity and the Arachidonic Acid Cascade in Kidney of Diabetic Rats\textsuperscript{1}

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ABSTRACT The purpose of the present study was to investigate the effects of vitamin E on microsomal phospholipase A\textsubscript{2} activity and the arachidonic acid cascade in the kidneys of streptozotocin (STZ)-induced diabetic rats. Sprague-Dawley male rats weighing 100±10 g were randomly assigned to one normal and three STZ-induced diabetic groups. The diabetic groups were fed a vitamin E–free diet (the DM-0E group), 40 mg vitamin E/kg diet (the DM-40E group) or a 400 mg vitamin E/kg diet (the DM-400E group). The kidney vitamin E concentrations were 59 and 49\% lower in the DM-0E and DM-40E groups, respectively, than in the normal group. The kidney thiobarbituric acid reactive substance concentrations in the DM-0E, DM-40E and DM-400E groups were 119, 84 and 33\% greater, respectively, than that in the normal group. The concentration in the DM-400E group was 39\% lower than that in the DM-0E group. The phospholipase A\textsubscript{2} (PLA\textsubscript{2}) activity in the kidney microsomes of the DM-0E-40E and DM-400E groups were 88, 58 and 35\% greater, respectively, than that in the normal group. The activity in the DM-400E group was 28\% lower than that in the DM-0E group and 16\% lower than that in the DM-40E group. The differences in the phospholipids in the kidney microsomes included reductions in the phosphatidylcholine and phosphatidylethanolamine compositions. Phosphatidylethanolamine hydrolysis in the kidney microsomes of the DM-0E and DM-40E groups were 84 and 64\%, which did not differ from the DM-400E group. The formation of thromboxane A\textsubscript{2} (TXA\textsubscript{2}) in the kidney microsomes was 137 and 70\% greater in the DM-0E and DM-40E groups, respectively, than in the normal group. TXA\textsubscript{2} formation did not differ between the DM-400E and normal groups. The formation of prostacyclin in the kidney microsomes was 60 and 44\% lower in the DM-0E and DM-40E groups, respectively, than in the normal group, whereas the DM-400E group did not differ from that in the normal group. The ratio of prostacyclin to TXA\textsubscript{2} was 82 and 65\% lower than normal in the DM-0E and DM-40E groups, respectively. Kidney function appears to be improved by vitamin E supplementation due to its antithrombus action, which in turn controls the arachidonic acid cascade system. J. Nutr. 131: 1297–1301, 2001.

KEY WORDS: • diabetes • vitamin E • antithrombus • phospholipase A • lipid peroxidation

The occurrence of diabetes has rapidly increased, especially in developed and developing countries, due to aging populations, obesity and unsound dietary habits. In most cases, diabetes is accompanied by triopathy, including retinopathy, nephropathy and neuropathy, and it is the cause of several other metabolic diseases. Therefore, diabetes often experience microvascular complications such as poor or loss of eyesight; cataracts; kidney failure; neuropathy in the arms, legs and brain; and serious vessel complications such as apoplexy, cardiac infraction and arteriosclerosis (Garcia et al. 1974, Kannel and Mcgee 1979, Patoa and Passa 1983). In particular, kidney disease, including kidney failure, has a high incidence rate, and once it occurs, there is no effective method of interrupting its progress. This complication has become a serious medical, social and economic problem; for example, it has been reported that 40–50\% of diabetics in Korea die of kidney failure (Choi and Lee 1995). Accordingly, the study of the mechanisms of microvascular dysfunction or impairment that cause kidney failure is very important. However, until now, few studies have focused on the nutritional aspects of the pathological mechanisms of diabetic kidney failure.

Klahr et al. (1988) conducted a pathohistiological study of kidney failure and renal arteriosclerosis and reported on the appearance of pathohistological changes such as the thickening of the glomerular basement membrane and expansion of the mesangium, followed by a decline in physiological function caused by damage to the glomeruli and renal tubules. In more recent studies on the functional damage of glomeruli and microvascular vessels such as renal tubules, it has been reported that the damage is related to eicosanoids, which are metabolites of arachidonic acid synthesized in the kidney cells (Choi and Yu 1996). In addition, the importance of vasodilatation by prostacyclin...
(PGI₂), a metabolite of arachidonic acid, and interaction with the renin-angiotensin system in the physiological functioning of the kidney has been observed (Brenner et al. 1989, Hostetter et al. 1986). Many other reports have revealed that eicosanoids affect the function of the kidney and that the excessive production of eicosanoids is related to various diseases. The eicosanoids synthesized in the kidney cells have an effect on renal hemodynamics, the glomerular filtration rate, sodium excretion, renin secretion and urinary concentration. In a normal kidney, the production of thromboxane A₂ (TXA₂) and PGI₂ is controlled, and the balance between them is important in maintaining homeostasis in vivo; for patients with chronic renal diseases, this balance is destroyed (Greene and Avasthi 1989, Remuzzi et al. 1985, Schlondorff and Avasthi 1986). Linos et al. (1983) reported that the glomeruli isolated from rats with nephritis induced by injecting an anti-glomerular basement antibody had TXA₂ synthesis that was 10 times higher than that from normal rats and that the excretion of urinary protein was greater in the nephrotic rats. It has also been observed that in the kidney of rats with glomerulosclerosis, the production of TXA₂ increases, whereas the production of PGI₂ decreases, resulting in an imbalance in the ratio of PGI₂ to TXA₂. PGI₂ dilates blood vessels, hinders platelet aggregation and prevents thrombogenesis, whereas TXA₂ stimulates vasoconstriction and produces thrombosis by accelerating platelet aggregation (Choi and Lee 1995); that is, PGI₂ elevates the glomerular filtration rate, whereas TXA₂ has the opposite effect. Therefore, the destruction of the balance of the PGI₂/TXA₂ ratio accelerates thrombogenesis in the renal tubules, arteriosclerosis and aging. Accordingly, rectifying this balance will result in an attenuation of renal arteriosclerosis, the proper control of renal hemodynamics and the glomerular filtration rate and an improvement of renal function, which ultimately can contribute to the prevention of diabetic kidney failure.

The production of TXA₂, PGI₂ and prostaglandin (PG)E₂ depends on the activity of phospholipase A₂ (PLA₂), a rate-limiting enzyme of the arachidonic acid (AA) cascade, plus the composition of the fatty acid that is a product of PLA₂ (Purkerson et al. 1976). PLA₂ activation depends on free radicals or oxidative stress such as lipid peroxidation. PLA₂ activation in tissues changes the level of eicosanoids through the activation of the AA cascade and then the activation of cyclooxygenase (Shivastava 1980). Therefore, if PLA₂ activity and the AA cascade can be controlled, this would reduce the damage to kidney tissues through oxidative stress and improve the function of the kidney.

Vitamin E in blood and tissues acts as an antioxidant that prevents the chain reactions of lipid peroxidation, removes the free radicals and then completes the chain reaction, thereby preventing the lipid peroxidation of polyunsaturated fatty acids in the cell membranes. Accordingly, it appears that vitamin E has an initial antioxidant function followed by an intensification of the antioxidant system. However, its antioxidative effect has been only partly established under pathophysiological conditions. Therefore, to provide basic research data for the development of substances related to the prevention and treatment of diabetic complications, the effect of vitamin E on PLA₂ activity and the AA cascade was investigated in the kidney of rats with diabetes that had been fed diets containing different levels of vitamin E for specified time periods.

**MATERIALS AND METHODS**

**Experimental animals and diets**

Male Sprague-Dawley rats weighing between 70 and 80 g were purchased from KRITC (Taejon, Korea). Rats were individually housed in stainless steel cages in a room with controlled temperature (20–23°C) and lighting (alternating 12-h periods of light and dark) and fed a pelleted commercial nonpurified diet (Samyang, Seoul, Korea) for 6 d after arrival. They were randomly divided into one normal group and three diabetic groups. The four groups (n = 10) fed experimental diets for 4 wk, and the diabetic groups were fed a vitamin E–free diet (the DM-0E group), 40 mg vitamin E/kg diet (the DM-40E group) or 400 mg vitamin E/kg diet (the DM-400E group). This experimental design was approved by the Committee of Catholic University of Taegu-Hyosung for the care and use of laboratory animals.

**Experimental diabetes.** Diabetes was induced by an intravenous injection of streptozotocin (STZ; 55 mg/kg body) in a citrate buffer (pH 4.5) via the tail vein. The rats with a blood glucose concentration of >16.7 mmol/L after 6 d were used for the experiment described here.

**Collection of samples and sample preparations.** The STZ diabetic rats were deprived of food for 12 h and killed on d 6. Their kidneys were excised, washed in 9 g/L NaCl, frozen rapidly in liquid nitrogen and stored at −80°C until use. The kidneys were homogenized in a buffer (10 mmol HEPES, 10 mmol KCl and 280 mmol sucrose per L, pH 7.4), centrifuged at 9000 × g for 15 min, reconstituted at 12,000 × g for 20 min to remove any contamination of mitochondria and then centrifuged at 105,000 × g for 60 min to yield the microsomal fraction.

**Measurement of vitamin E concentrations**

The vitamin E concentrations of the kidney microsomes were determined according to the method of Kayden et al. (1973). Briefly, the preparation of kidney microsomes was performed as previously described. Five mL of 20 g pyrogallol/L was added to the microsomes on heating. After being mixed, incubated at 70°C for 2 min and mixed with 0.3 mL KOH, the microsomes were then incubated at 70°C for an additional 30 min. The incubated microsomes were cooled in an ice bath, mixed with 4 mL distilled H₂O and 10 mL hexane and then vigorously vortexed for 2 min. After centrifugation at 1500 × g for 10 min, 7 mL of the resultant was used for the vitamin E extraction. The extract was dried with N₂ gas and mixed with 0.8 mL of 5 g ferric chloride/L and 0.8 mL of 5 g dipiryldil/L. After vortexing, 2 mL ethanol and ferric chloride was added to the mixture, and the optical density of the color formed was measured at 520 nm.

**Separation and measurement of phospholipid species: lipid extraction and determination of phosphorus**

The lipids were extracted according to the method of Bligh and Dyer (1959). A mixture of chloroform/methanol/H₂O (1:1:1, v/v/v) was added to the kidney microsomes, and then the mixtures were stirred vigorously and centrifuged. The chloroform fractions obtained were vaporized with N₂ gas to form a lipid film. The determination of the phosphorus included in the extracted lipids was carried out according to the method of Marinetti (1962).

**Separation of phospholipid species**

A two-dimensional TLC was used to separate the phospholipid. A mixture of chloroform/methanol/acetic acid (65:25:10, v/v/v) was used as the first developing solvent, and a mixture of chloroform/methanol/formic acid (88%) (65:25:10, v/v/v) was used as the second developing solvent. The separated lipids on the TLC plate (No. 5721; Merck, 20 × 20 cm, silica gel 60, without a fluorescent indicator) were detected with I₂ vapor and then redetected with ninhydrin. The phospholipid species such as phosphatidylcholine (PC), lysophosphatidylcholine (lysPC), phosphatidylethanolamine (PE) and lyso-
TABLE 1

<table>
<thead>
<tr>
<th>Group</th>
<th>Kidney</th>
<th>Vitamin E</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>g</td>
<td>g/100 g body</td>
</tr>
<tr>
<td>Normal</td>
<td>2.255 ± 0.067&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.702 ± 0.025&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>DM-0E</td>
<td>2.736 ± 0.083&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.036 ± 0.037&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>DM-40E</td>
<td>2.767 ± 0.101&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.039 ± 0.038&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>DM-400E</td>
<td>2.604 ± 0.089&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.951 ± 0.035&lt;sup&gt;a&lt;/sup&gt;</td>
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</table>

<sup>1</sup> Means ± se, n = 10. Values in a column with different superscript letters are significantly different, P < 0.05.

RESULTS

Kidney weights and vitamin E concentrations. Kidneys of the DM-0E, DM-40E and DM-400E groups were significantly heavier than that of the normal group. However, there were no significant differences among the diabetic groups (Table 1).

Kidney microsomal vitamin E concentrations of the DM-0E and DM-40E groups were 59 and 49% lower, respectively, than in the normal group, which did not differ from the DM-400E group (Table 1).

PLA<sub>2</sub> activity in kidney microsomes. The kidney microsomal PLA<sub>2</sub> activity in the DM-0E, DM-40E and DM-400E groups was 88, 58 and 35% greater, respectively, than that in the normal group (Fig. 1).

Level of TBARS in kidney tissues. The kidney TBARS concentrations, an index of lipid peroxidation, were 119, 84 and 33% greater in the DM-0E, DM-40E and DM-400E groups, respectively, compared with the normal group (Fig. 2).

PC and PE hydrolyzed in kidney microsomes. The percentage of PC hydrolyzed in the kidney microsomes of the DM-0E group was 52% greater than that of the normal group, whereas in the DM-40E and DM-400E groups, it did not differ from the normal group (Table 2). The percentage of PE hydrolyzed in the kidney microsomes of the DM-0E and DM-40E groups was 84 and 64% greater, respectively, than that of the normal group, whereas the DM-400E group did not differ (Table 2).

Production of TXA<sub>2</sub> and PGI<sub>2</sub> in kidney microsomes. The formation of TXA<sub>2</sub> in the kidney microsomes was 137 and 70% greater in the DM-0E and DM-40E groups, respectively, than in the normal group; however, the DM-400E and control groups did not differ (Fig. 3A). The formation of PGI<sub>2</sub> in the kidney microsomes was 60 and 44% lower in the DM-0E and DM-40E groups, respectively, than in the normal group, which did not differ from the DM-400E group (Fig. 3B). The ratio of PGI<sub>2</sub>/TXA<sub>2</sub> (Fig. 3C) was 82 and 65% lower in the DM-0E and DM-40E groups, respectively, than in the normal group, whereas the ratio in the DM-400E group did not differ from that in the normal group (Fig. 3C).

DISCUSSION

The purpose of this study was to investigate the effects of vitamin E on microsomal PLA<sub>2</sub> activity and the AA cascade in the kidneys of STZ-induced diabetic rats.

The formation of free radicals is part of normal metabolism. However, in diabetics, the production of these free radicals is accelerated due to abnormal metabolic regulation, which results in oxidative damage (Hoguchi 1982). The system of free radical generation includes xanthine oxidase or a mixed func-

FIGURE 1

Effect of 0 (DM-0E), 40 (DM-40E) or 400 (DM-400E) mg vitamin E/kg diet on kidney microsomal phospholipase A<sub>2</sub> (PLA<sub>2</sub>) activity in streptozotocin-induced diabetic rats. All values are mean ± se, n = 10; values with different superscript letters are significantly different, P < 0.05.
tion oxidase system. PLA$_2$ also functions in the generation of free radicals. The increase in PLA$_2$ activity accelerates the production of free AA (Panganamala and Cornwell 1982) and attenuates the lipoxygenase and cyclooxygenase systems, which are both pathways of the AA cascade. Therefore, free radicals may be produced during this metabolic process, which can then reactivate the PLA$_2$ (Gwebu et al. 1980, Panganamala and Cornwell 1982).

In this study, the activity of PLA$_2$, a rate-limiting enzyme of the AA cascade, was measured in the kidney microsomes of STZ-induced diabetic rats supplemented with different levels of vitamin E. Vitamin E supplementation decreased the PLA$_2$ activity in these diabetic rats with reduction proportional to the amount of vitamin E supplemented in the present study. Cytosolic PLA$_2$ activity is generally decreased by the activation of protein kinase C in persons with diabetes mellitus (Hidehiro et al. 1998). These results are similar to those mentioned in the reports of Rhee et al. (1995) and Prichard et al. (1982), where the dietary supplementation of vitamin E in rabbits inhibited the PLA$_2$ activity and decreased the concentration of the kidney lipid peroxides. This means that in the diabetic rats, the AA concentration is increased along with PLA$_2$ activity in the cell membrane. Vitamin E inhibited the production of lipid peroxides in the tissues, thereby inhibiting the PLA$_2$ activity due to its antioxidative action. Diabetes significantly increased AA in rat kidneys according to the study of Douillet et al. (1998).

Stephen et al. (1989) reported that when a biomembrane is exposed to a free radical production system, the level of endog-

![Figure 2](image2.png)

**FIGURE 2** Effect of 0 (DM-0E), 40 (DM-40E) or 400 (DM-400E) mg vitamin E/kg diet on kidney thiobarbituric acid reactive substance (TBARS) concentrations in streptozotocin-induced diabetic rats. MDA, malondialdehyde. All values are mean ± SE, n = 10; values with different superscripts are significantly different, P < 0.05.

![Figure 3](image3.png)

**FIGURE 3** Effect of 0 (DM-0E), 40 (DM-40E) or 400 (DM-400E) mg vitamin E/kg diet on kidney microsomal thromboxane A$_2$ (TXA$_2$) (A) and prostacyclin (PGI$_2$) (B) synthesis and the PGI$_2$/TXA$_2$ ratio (C) in streptozotocin-induced diabetic rats. All values are mean ± SE, n = 10; values with different superscripts are significantly different, P < 0.05.

![Table 2](table2.png)

**TABLE 2**

<table>
<thead>
<tr>
<th>Group</th>
<th>PC hydrolyzed$^2$</th>
<th>PE hydrolyzed$^3$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>6.878 ± 0.844$^b$</td>
<td>9.224 ± 1.373$^b$</td>
</tr>
<tr>
<td>DM-0E</td>
<td>10.452 ± 0.904$^a$</td>
<td>17.099 ± 1.886$^a$</td>
</tr>
<tr>
<td>DM-40E</td>
<td>8.178 ± 0.904$^b$</td>
<td>15.168 ± 0.681$^b$</td>
</tr>
<tr>
<td>DM-400E</td>
<td>8.142 ± 1.026$^b$</td>
<td>13.821 ± 2.401$ab$</td>
</tr>
</tbody>
</table>

$^1$ Means ± SE, n = 10. Values in a column with different superscripts differ, P < 0.05.

$^2$ [lysOPC/(PC + lysPC)] × 100.

$^3$ [lysOPE/(PE + lysOPE)] × 100.

$^4$ DM-0E, DM-40E and DM-400E indicate diabetic rats fed 0, 40 and 400 mg vitamin E/kg diet, respectively.

Enous lysophospholipid increases. In this study, differences in the phospholipid species, such as PC, lysPC, PE and lysoPE, were observed in the kidney microsomes of diabetic rats supplemented with different levels of vitamin E. The most common difference was seen with PC and PE. In the DM-0E group, the percentage of PC and PE hydrolyzed was 50–53%; the PE in the kidney microsomes was hydrolyzed more than the PC. The percentage of PC and PE hydrolyzed was higher in the DM-40E group than in the normal group. However, the DM-400E group, supplemented with a high level of vitamin E, did not differ from the normal group. Accordingly, it appears that the dietary supplementation of a high concentration of vitamin E decreased the hydrolysis of the phospholipids in the cell membrane of the diabetic kidney tissues. This result is similar to the study of Choi et al. (1998) that showed the hydrolysis of the phospholipids in the cell membrane of liver tissues of diabetic rats was lower than that of normal rats and that there was no significant difference in the PC hydrolysis, although PE hydrolysis was higher in the diabetic group than in the normal group. Accordingly, it appears that the increase in the PE hydrolysis is due to the selective hydrolysis of PE by PLA$_2$. In addition, the lowered PE hydrolysis in vitamin E supplementation was related to the increase in the PLA$_2$ activity, which can also be attributed to the vitamin E supplement.

TXA$_2$, PGI$_2$ and PGE$_2$ are produced from AA via cyclooxygenase. Klahr (1988) previously reported that thromboxane and prostacyclin, which function as vasoconstrictors and vasodilators, respectively, are synthesized in the kidney and have an effect on kidney function by controlling renal hemodynamics and the glomerular filtration rate. In particular, TXA$_2$...
functions as a strong accelerator of vasoconstriction and thrombogenesis and exacerbates kidney disease by constricting mesangial cells and reducing the glomerular filtration rate. In the case of diabetes, decreased PGI2 and increased TXA2 production tends to produce an increased platelet susceptibility, which results in the induction of excessive platelet agglutination and the frequent pathogenesis of microvascular complications (Shohat and Boner 1993).

In this study, the amount of TXA2 synthesized in the kidney microsomes was higher in the DM-0E group than in the normal group. The level of TXA2 synthesized in the DM-40E group was significantly lower than that in the DM-0E group (P < 0.05), whereas the DM-40E group had almost the same level of synthesized TXA2 as the normal group. The level of PGI2 synthesized in the kidney microsomes was significantly lower in the DM-0E and DM-40E groups (P < 0.05) than in the normal group; however, the DM-40E group had the same level of synthesized PGI2 as the normal group. In another study, the vitamin E and Se supplementation increased 20:5(n-3), a precursor of PGI2, in the aorta of diabetic rats (Douillet et al. 1998). Sushill et al. (1998) also reported that the supplementation with modest doses of vitamin E (100 IU/d) significantly lowered blood TXB2 and lipid peroxidation product levels in type I diabetic patients. The PGI2/TXA2 ratio, which is an important element in determining the thrombogenic index and risk of vasoconstriction, was reduced in the diabetic groups; however, the ratio increased in proportion to the level of dietary vitamin E supplementation. This result is supported by the report of Karpen et al. (1987), in which an imbalance in the PGI2/TXA2 ratio was improved by a sufficient amount of dietary vitamin E was identified as a potential healing substance for increasing aortic PGI2 and reducing platelet TXA2 and as an endogenous factor related to the etiology of diabetic vascular disorders. Patricia et al. (1991) reported that an imbalance of PGI2 and TXA2 in the platelets of diabetic rats is due to the sensitive inhibition of prostacyclin synthetase activity by lipid peroxides.

In this study, the kidney microsomal vitamin E concentration in the DM-40E group, with a large amount of vitamin E supplementation, was 1.1 times higher than that in the DM-0E group, the vitamin E-free group. In addition, correlations of the vitamin E concentration with both the PLA2 activity and the PGI2/TXA2 ratio in the kidney microsomes was high. Accordingly, dietary vitamin E supplementation had an influence on these important factors. The vitamin E may restore depressed PGI2 production under hyperglycemic conditions (Kunisaki et al. 1992).

In conclusion, dietary vitamin E reduced the increased concentration of lipid peroxides in the kidney tissues of diabetic rats by decreasing their elevated PLA2 activity and PE hydrolysis. Dietary vitamin E also improved the PGI2/TXA2 balance in the kidney microsomes of diabetic rats by decreasing TXA2 synthesis and increasing PGI2 synthesis in proportion to the level of the dietary vitamin E. Therefore, we suggest that dietary vitamin E can improve diabetic renal vascular disorders.

LITERATURE CITED


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