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Renal lesions in streptozotocin-induced diabetic rats maintained on onion and capsaicin containing diets

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Onion (Allium cepa) powder and capsaicin, the pungent principle of red pepper (*Capsicum annum*) were added in the amounts of 3 g% and 15 mg%, respectively, to the diet of streptozotocin-induced diabetic Wistar rats for 8 weeks. The presence of renal lesions was assessed by the extent and quality of proteinuria and by the leaching of renal tubular enzymes into the urine. Renal integrity was assessed by measuring the activities in the kidney tissue of several key enzymes of carbohydrate metabolism and of polyol pathway, transaminases, and ATPases. Data on enzymuria and proteinuria, activities of kidney ATPases present in diabetic patients, suggested that dietary onion caused significant beneficial modulation of the progression of renal lesions in the diabetic rats. These findings were also corroborated by histologic examination of kidney sections. Dietary capsaicin did not have any favorable influence on renal pathology in diabetes. It is inferred that this beneficial ameliorating influence of dietary onion on diabetic nephropathy may be mediated through onion's ability to lower blood cholesterol levels and to reduce lipid peroxidation. (J. Nutr. Biochem. 10:477–483, 1999)

Keywords: diabetes mellitus; renal lesions; onion; capsaicin

Introduction

Diabetic nephropathy is one of the most frequent complications of diabetes mellitus, which usually develops in 30 to 40% of patients with insulin dependent diabetes mellitus (IDDM), and terminal renal failure occurs within 7 years after the onset of renal disease.[1] Kidney disease is usually attributed to metabolic consequences of abnormal glucose regulation such as elevated blood and tissue levels of glycosylated proteins, to hemodynamic changes within the kidney tissue, and to increases in oxidative stress.[2] There has been a renewed interest in understanding the possibility of abnormalities in lipid metabolism that contribute to the pathogenesis of progressive renal disease.[3] The important role of lipid abnormalities in the pathogenesis of glomerular injury is understood by the almost invariable presence of hyperlipidemia in patients with renal disease.[4] The degree of lipid and lipoprotein abnormalities correlates directly with the severity of proteinuria, because the magnitude of proteinuria roughly parallels the rate of deterioration in renal function.[4,5]

Although controlling blood glucose level is the most important approach in the management of diabetic nephropathy,[6] other strategies have been proposed to offer specific advantages. Treatment of hypercholesterolemia has been shown to reduce diabetic nephropathy.[5] New kinds of drugs such as aldose reductase inhibitors[7] and angiotensin converting enzyme inhibitors[8] also may reduce the diabetic kidney complications. Diet is the mainstay of management of diabetes mellitus at all stages of the disease. If a suitable dietary intervention could reduce the ensuing diabetic kidney complications, it would become the most acceptable and powerful tool in the management of this disease.

The widely consumed spices red pepper (*Capsicum annum*) and onion (*Allium cepa*) are known to have a cholesterol-lowering influence in hyperlipidemic experimental animals and humans.[9,10] In a previous study, we reported that dietary curcumin (the coloring principle of turmeric) has a significant cholesterol-lowering ability in diabetic rats,[11] and by virtue of this, the spice principle also

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showed a beneficial ameliorating influence on renal tubular lesions.[12] We also have observed that onion has both hypoglycemic and hypocholesterolemic effects in diabetic patients.[13] Capsaicin from red pepper does not have any significant hypolipidemic influence in streptozotocin-induced diabetic rats.[13] In the present investigation, we have extended our study to determine whether these dietary spices—onion and capsaicin—by virtue of their cholesterol-lowering ability or otherwise, would modulate the renal lesions associated with diabetes in experimental animals.

Methods and materials

Chemicals

Streptozotocin, glucose oxidase, horseradish peroxidase, o-dianisidine, p-nitrophenyl phosphate, p-nitrophenyl-N-acetyl-β-D-glucosaminidine, glucose-6-phosphate, D(−)fructose, pyruvic acid, ouabain, sodium dodecyl sulfate (SDS), adenosine triphosphate (ATP), Nicotinamide adenine dinucleotide phosphate (β-NADP), Nicotinamide adenine dinucleotide-reduced (β-NADH), Nicotinamide adenine dinucleotide phosphate-reduced (β-NADPH), malate dehydrogenase, DL-alanine, L-aspartic acid, 2-oxoglutaric acid, triethanolamine, and Tris-HCl were obtained from Sigma Chemical Co. (St. Louis, MO USA). Commassie brilliant blue was obtained from Eastman Kodak Co. (Rochester, NY USA). Acrylamide and bis-acrylamide were obtained from Merck Co. (Germany), and ammonium persulfate was obtained from LKB (Sweden). All other chemicals were of analytical grade and were obtained from M/s. Qualigens Fine Chemicals (Bombay, India). All solvents were distilled prior to use.

Spices

Capsaicin (8-methyl-N-vanillyl nonenamide) was obtained from Sigma Chemical Co. Onion procured from local market was finely minced and freeze dried (powder yield was 12% of fresh onions).

Animals

Male albino Wistar rats weighing 120 to 130 g and raised in Experimental Animal Production Unit of our institute were used in this investigation. The animals were housed individually in stainless steel metabolic cages. Experimental diabetes was induced by a single intraperitoneal injection of streptozotocin at a dose of 60 mg/kg body weight (1 mL freshly prepared solution in 0.1 M citrate buffer, pH 4.5) to animals fasted overnight; control rats were injected with the citrate buffer alone. The rats had free access to 5% glucose water and ad libitum basal diet during the next 24 hours. Blood samples were obtained from the retroorbital plexus in both streptozotocin-injected and control animals at 72 hours after an overnight fast. Fasting blood glucose levels were determined by glucose oxidase method.[14] Rats with fasting blood glucose levels above 225 mg/dL were used as diabetic animals.

Three groups of diabetic rats (12 rats each) and a parallel three groups of control animals were maintained on various experimental diets ad libitum for 8 weeks. The basal diet consisted of (%): casein, 21; cane sugar, 10; corn starch, 54; refined peanut oil, 10; NRC vitamin mixture, 1; and Bernhart-Tomarelli salt mixture, 4. The spice diets consisted of either 3 g% onion powder or 15 mg% capsaicin replacing an equivalent amount of starch from the basal composition. Urine samples were collected toward the end of the feeding schedule, stored in ice-cold bottles for 24 hours, clarified by filtration, and used for various enzyme analyses. At the end of 8 weeks, the animals were euthanized by exsanguination from the heart under diethyl ether anesthesia; the kidney was quickly excised and processed for enzyme assays.

Enzyme assays

Alanine aminotransferase in urine and kidney homogenate was assayed according to the colorimetric method of Reitman and Frankel as described by Bergmeyer and Bernt.[15] Aspartate aminotransferase activity in kidney homogenate was measured by the spectrophotometric method of Bergmeyer and Bernt[16] by following the rate of NADH oxidation in the reaction. Aspartate aminotransferase activity in urine was measured by the colorimetric method of Reitman and Frankel involving measurement of 2,4-dinitrophenyl hydrazone of the reaction product oxaloacetate formed during the reaction.[17]

Phosphatase activities in kidney homogenates and urine were determined according to the method of Walter and Schult,[18] using p-nitrophenyl phosphate as substrate. Urinary N-acetyl-β-glucosaminidase (NAG) activity was assayed by the method described by Maruhn,[19] by measuring the amount of p-nitrophenol formed from the hydrolysis of p-nitrophenyl-N-acetyl glucosaminidine by the enzyme. Lactate dehydrogenase (LDH) in kidney homogenates and urine was assayed by the method of Bergmeyer and Bernt,[20] following the rate of oxidation of NADH during the reaction.

Glucose-6-phosphate dehydrogenase in kidney homogenate was measured according to the method described by Lohr and Waller,[21] following the rate of formation of NADPH during the reaction. Glucose-6-phosphatase activity was determined according to the procedure described by Baginski et al.,[22] estimating the inorganic phosphorus liberated during the reaction by the method of Taussky and Shorr.[23] Aldose reductase activity in renal homogenates was determined by the procedure of Patricia,[24] involving measurement of decrease in absorption at 340 nm due to oxidation of $NADPH_2$. Sorbitol dehydrogenase activity was determined by the modified method of Gerlach and Hiby,[25] following the rate of oxidation of NADH. Na^+, K^+-ATPase activity was measured by the method of Jorgenson,[26] quantitating inorganic phosphate released from the substrate ATP,[23] and Mg^{++}, Ca^{++}-ATPase was determined by the method of Recknagel and Anthony.[27]

SDS-PAGE analysis of urinary proteins

Proteins in urine samples collected during the last 24 hours of experimental duration were precipitated with 3% TCA. The protein precipitate obtained by centrifugation was redissolved in sample buffer and was subjected to SDS-PAGE on 12% acrylamide gels along with standard marker proteins in presence of β-mercaptoethanol.[28] The protein bands were visualized by staining with Coomassie blue followed by destaining. The protein bands in each sample lane were quantitated by scanning in a Gel Ultra Scanner (LKB Model XL, LKB Products, Sweden).

Histologic studies

Light microscopic studies were carried out with hematoxylin-eosin–stained thin sections of kidney previously fixed in 10% formalin and embedded in paraffin.

Protein in kidney homogenates was quantitated by the modified Lowry's procedure.[29] Creatinine in urine samples was determined by the alkaline picrate method.[30] Results are expressed as mean ± SEM and comparisons between groups were made by subjecting the data to analysis of variance appropriate to a completely randomized design with 12 rats per group. The mean values were separated by using Duncan's new multiple range test,[31] and differences were considered significant when the *P*-value was less than 0.05.

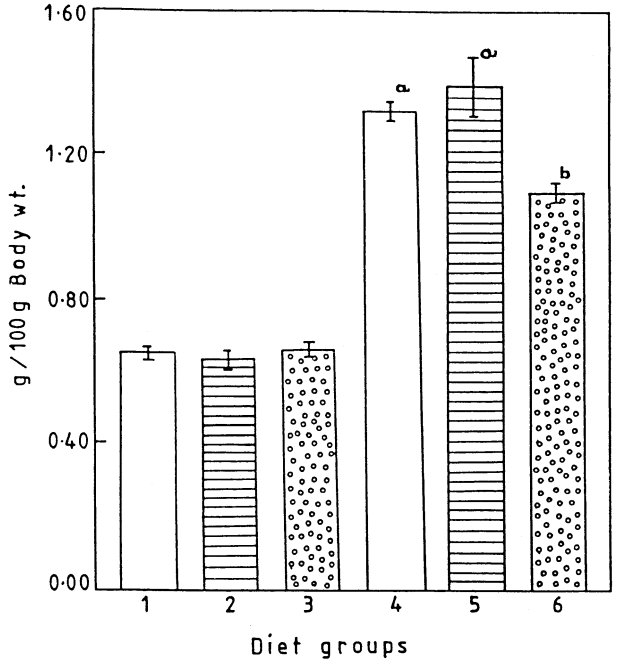

Figure 1 Influence of dietary onion and capsaicin on kidney weights in diabetic rats. Diet groups: 1, normal-control; 2, normal-capsaicin; 3, normal-onion; 4, diabetic-control; 5, diabetic-capsaicin; 6, diabetic-onion. Values are mean + SEM of 12 animals in each group. Values with same superscript are statistically, but not significantly different at $P < 0.05$.

Results

Diabetic rats were characterized by markedly large kidneys, the organ weights of which were approximately two times those of normal controls (*Figure 1*). Diabetic animals maintained on the onion diet showed a significant decrease (17%) in kidney weight compared with those animals maintained on the control diet. However, in nondiabetic animals there was no difference in kidney weights in different dietary groups. Capsaicin had no influence on the nephromegaly of diabetic rats.

Urinary enzymes

Influence of dietary onion and capsaicin on the leaching of renal tubular enzymes in diabetic rats is presented in *Tables 1 and 2*. Enzymes of proximal tubular origin (i.e., NAG, alkaline phosphatase, and alanine aminotransferase) were excreted in significantly large quantities under diabetic conditions (*Table 1*). Diabetic animals maintained on the onion diet showed a distinct tendency to excrete smaller amounts of these proximal tubular enzymes in the urine, the decrease in leaching of these enzymes being 18, 40, and 35%, respectively. Diabetic rats also excreted large amounts of enzymes of distal tubular origin in the urine (*Table 2*). Leaching of LDH, aspartate aminotransferase, and acid phosphatase was comparatively less in diabetic animals maintained on the onion diet, enzyme excretion being 23, 40, and 32% less, respectively. Dietary capsaicin did not show any appreciable influence on excretion of renal tubular enzymes by diabetic animals.

Table 1 Leaching of renal tubular enzymes (proximal region) in diabetic rats maintained on onion and capsaicin diets

Group/Diet	Alanine aminotransferase*	Alkaline phosphatase†	NAG‡
Normal			
Control	6.92 ± 0.74[a]	0.010 ± 0.001[a]	0.113 ± 0.007[a]
Onion	7.95 ± 0.64[a]	0.011 ± 0.001[a]	0.098 ± 0.005[a]
Capsaicin	6.46 ± 0.66[a]	0.012 ± 0.001[a]	0.097 ± 0.006[a]
Diabetic			
Control	23.91 ± 1.98[b]	0.131 ± 0.008[b]	0.796 ± 0.039[b]
Onion	15.62 ± 1.04[c]	0.078 ± 0.010[c]	0.655 ± 0.045[c]
Capsaicin	20.72 ± 2.04[b]	0.122 ± 0.010[b]	0.802 ± 0.033[b]

Values are mean ± SEM of 12 animals per group.
Specific activity units: *μg pyruvate released/min/mg creatinine; †μmol p-nitrophenol formed/min/mg creatinine; ‡μmol p-nitrophenol formed/min/mg creatinine.
[abc]Values with same superscript are statistically, but not significantly, different at $P < 0.05$.
NAG–N-acetyl-β-glucosaminidase.

Urinary protein profiles

Urinary protein profiles of various dietary groups were monitored by SDS-PAGE, which revealed that all diabetic rats excreted large amounts of proteins with molecular weights of around 66K and proteins of molecular weights still higher (*Figure 2*). Onion fed diabetic rats excreted these proteins to a much lesser extent compared with those on the control diet. The relative percentage of total excreted proteins in the onion group was 24% of 66K proteins compared with the 68% in the control group; and 3% of proteins in the onion fed group had a molecular weight greater than 66K compared with 17% in the control group. Dietary capsaicin in diabetic rats did not influence the excretion of either 66K protein or proteins of still higher molecular weights, which remained comparable to those of the control group.

Kidney enzymes

The influence of dietary onion and capsaicin on kidney tissue enzymes in diabetic rats are presented in *Tables 3, 4,*

Table 2 Leaching of renal tubular enzymes (distal region) in diabetic rats maintained on onion and capsaicin diets

Group/Diet	Aspartate aminotransferase*	Acid phosphatase†	LDH‡
Normal			
Control	0.490 ± 0.092[a]	0.009 ± 0.001[a]	0.032 ± 0.004[a]
Onion	0.543 ± 0.045[a]	0.011 ± 0.001[a]	0.039 ± 0.004[a]
Capsaicin	0.578 ± 0.107[a]	0.010 ± 0.001[a]	0.031 ± 0.003[a]
Diabetic			
Control	18.5 ± 1.73[b]	0.062 ± 0.010[b]	0.308 ± 0.021[b]
Onion	10.8 ± 1.38[c]	0.042 ± 0.007[c]	0.238 ± 0.016[c]
Capsaicin	16.6 ± 2.44[b]	0.058 ± 0.008[b]	0.327 ± 0.018[b]

Values are mean ± SEM of 12 animals per group.
Specific activity units: *μg pyruvate released/min/mg creatinine; †μmol p-nitrophenol formed/min/mg creatinine; ‡ΔE/min/mg creatinine.
[abc]Values with same superscript are statistically, but not significantly, different at $P < 0.05$.
LDH–lactate dehydrogenase.

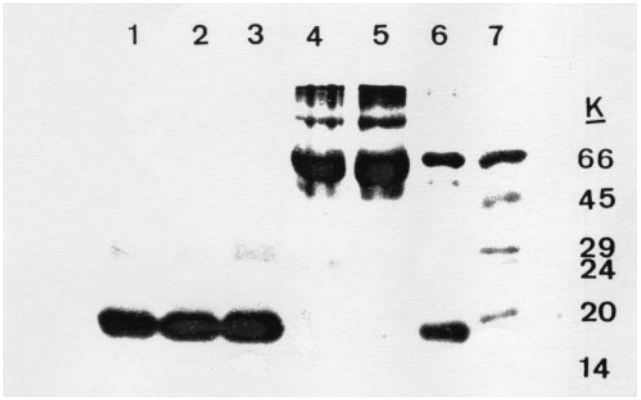

Figure 2 SDS-PAGE profile of urinary proteins in diabetic rats fed onion and capsaicin diets. Lanes: 1, normal-control; 2, normal-capsaicin; 3, normal-onion; 4, diabetic-control; 5, diabetic-capsaicin; 6, diabetic-onion; 7, marker proteins.

and 5. Activities of glucose-6-phosphatase and LDH were increased in the kidneys of diabetic animals (26% and 25% of normal controls, respectively), whereas that of glucose-6-phosphate dehydrogenase was significantly lower (41%; *Table 3*). Dietary onion caused a significant improvement on these enzymes of carbohydrate metabolism in the renal tissue of diabetic animals, countering the increase in the activities of glucose-6-phosphatase and LDH activity. Similarly, the increases in the activities of enzymes of the polyol pathway (i.e., aldose reductase and sorbitol dehydrogenase; 100% and 27%, respectively) that were caused by the diabetic condition were partially countered by dietary onion (32% and 14%, respectively; *Table 3*). Capsaicin feeding did not have any influence on these renal enzymes of diabetic animals.

Diabetic rats exhibited higher activities of renal aminotransferases and phosphatases compared with normal animals (*Table 4*). Aspartate and alanine aminotransferases were 40% and 63% higher, respectively, whereas alkaline and acid phosphatases were 33% and 26% higher, respectively, in diabetic animals. Dietary onion produced a significant decreases in aminotransferase and phosphatase activities in diabetic animals. The reversal of diabetes-induced enzyme activity changes were 20, 16, 12.5, and 21% lower as a result of onion feeding.

Diabetic rats were characterized by a significant reduction in activities of Na^+, K^+-ATPase, Mg^{++}-ATPase, and Ca^{++}-ATPase in renal membrane compared with normal animals (*Table 5*). The decreases in these ATPase activities were 43, 24.5, and 36.5%, respectively. Onion feeding to diabetic animals produced a significant reversal in this alteration of ATPases activity. Diabetic rats maintained on the onion diet had 37, 19, and 32% higher activity of these ATPases, respectively, than animals maintained on the control diet. However, dietary capsaicin did not offer any beneficial reversal of renal ATPase activities in diabetic rats.

Histopathology of kidney sections

Histologic examination of the kidney sections revealed pronounced glomerulosclerosis and tubular lesions and cellular infiltration in all diabetic rats maintained on the control diet. Dietary onion produced a decrease in the severity of these renal pathologies in diabetic rats when compared with those fed the control diet (not shown). Dietary capsaicin did not have any beneficial effect on kidney pathology in diabetic rats.

Discussion

High blood cholesterol is a risk factor for declining kidney function in patients with diabetic nephropathy. Patients with diabetic nephropathy and a low serum cholesterol concentration are reported to exhibit a lower degree of kidney lesions than those patients with a high serum cholesterol concentration.[5] The objective of the present study was to examine whether supplementation of spices in the diet, which have the potential to cause a hypolipidemic effect, would influence renal abnormalities in diabetic rats by virtue of their cholesterol lowering effect.

Nephromegaly is a typical feature and one of the early signs of diabetic nephropathy.[32] In the present study, a diet containing onion dramatically lowered kidney weights in diabetic rats, which are otherwise characterized by relatively large kidneys. The diet containing capsaicin had no

Table 3 Influence of dietary onion and capsaicin on renal enzymes of carbohydrate metabolism and polyol pathway in diabetic rats

Group/Diet	Glucose-6P-dehydrogenase*	Glucose-6-phosphatase†	Lactate dehydrogenase*	Aldose reductase*	Sorbitol dehydrogenase*
Normal					
Control	$0.082^a \pm 0.006$	$23.4^a \pm 0.76$	$1.72^a \pm 0.006$	$0.030^a \pm 0.002$	$0.250^a \pm 0.012$
Onion	$0.076^a \pm 0.002$	$24.3^a \pm 1.12$	$1.75^a \pm 0.020$	$0.030^a \pm 0.003$	$0.258^a \pm 0.014$
Capsaicin	$0.088^a \pm 0.002$	$24.2^a \pm 1.15$	$1.80^a \pm 0.047$	$0.032^a \pm 0.004$	$0.248^a \pm 0.022$
Diabetic					
Control	$0.048^b \pm 0.002$	$31.6^b \pm 0.55$	$2.22^b \pm 0.031$	$0.061^b \pm 0.002$	$0.317^b \pm 0.015$
Onion	$0.066^c \pm 0.002$	$26.6^a \pm 0.13$	$1.94^c \pm 0.064$	$0.042^c \pm 0.005$	$0.275^c \pm 0.003$
Capsaicin	$0.042^b \pm 0.003$	$29.3^b \pm 0.24$	$2.18^b \pm 0.052$	$0.056^b \pm 0.004$	$0.312^b \pm 0.026$

Values are mean ± SEM of 12 animals per group.
Specific activity units: *ΔE/min/mg protein; †μmol Pi released/min/mg protein.
[abc]Values with same superscript are statistically, but not significantly, different at $P < 0.05$.

Table 4 Influence of dietary onion and capsaicin on renal aminotransferases and phosphatases in diabetic rats

Group/Diet	Aspartate aminotransferase*	Alanine aminotransferase†	Alkaline phosphatase‡	Acid phosphatase‡
Normal				
Control	0.605[a] ± 0.024	9.95[a] ± 0.55	0.192[a] ± 0.008	0.108[a] ± 0.006
Onion	0.610[a] ± 0.039	9.75[a] ± 1.12	0.201[a] ± 0.019	0.108[a] ± 0.006
Capsaicin	0.590[a] ± 0.031	9.46[a] ± 0.28	0.190[a] ± 0.016	0.103[a] ± 0.016
Diabetic				
Control	0.852[b] ± 0.074	17.7[b] ± 0.54	0.253[b] ± 0.008	0.156[b] ± 0.003
Onion	0.689[c] ± 0.055	14.9[c] ± 0.43	0.222[c] ± 0.010	0.124[c] ± 0.006
Capsaicin	0.855[b] ± 0.100	16.5[b] ± 0.64	0.240[b] ± 0.018	0.138[b] ± 0.006

Values are mean ± SEM of 12 animals per group.
Specific activity units: *ΔE/min/mg protein; †μg pyruvate released/min/mg protein; ‡μmol p-nitrophenol formed/min/mg protein.
[abc]Values with same superscript are statistically, but not significantly, different at $P < 0.05$.

effect. Albuminuria is another characteristic feature of diabetes mellitus and marked albuminuria was exhibited by all diabetic rats in the present study. Proteins from the kidney appear in the urine as a consequence of normal process of cell turnover and metabolism. The release of these proteins is enhanced during the kidney's functional impairment, as happens in diabetes. The present study reveals that the excretion of 66K albumin/s and of proteins with a molecular weight higher than this, which are derived from damaged kidneys,[33] were considerably decreased by dietary onion in diabetic rats. Partial reversal of nephrotic syndromes has been reported in patients treated with hypocholesterolemic drugs.[34]

The extent of renal tubular lesions in diabetic animals was assessed by measuring the activity of certain renal tubular enzymes excreted in the urine. Enzymuria has been successfully used as an index to detect drug-induced nephropathies.[35] In the present study, proximal tubular lesions were assessed by measuring the excretion of the enzymes NAG, alanine aminotransferase, and alkaline phosphatase; urinary LDH, aspartate aminotransferase, and acid phosphatase were the enzymes of distal tubular origin that were monitored. The onion-supplemented diet had a favorable decreasing influence on the leaching of these marker enzymes of both proximal and distal origins in diabetic rats, but this effect was not seen in capsaicin-supplemented animals.

Table 5 Influence of dietary onion and capsaicin on kidney ATPase activities in diabetic animals

Group/Diet	Na^+, K^+-ATPase	Mg^{++}-ATPase	Ca^{++}-ATPase
Normal			
Control	0.282 ± 0.014[a]	0.171 ± 0.016[a]	0.224 ± 0.012[a]
Onion	0.255 ± 0.028[a]	0.165 ± 0.014[a]	0.218 ± 0.016[a]
Capsaicin	0.272 ± 0.020[a]	0.156 ± 0.018[a]	0.230 ± 0.018[a]
Diabetic			
Control	0.160 ± 0.013[b]	0.107 ± 0.008[b]	0.170 ± 0.010[b]
Onion	0.220 ± 0.005[c]	0.142 ± 0.010[c]	0.202 ± 0.010[c]
Capsaicin	0.185 ± 0.014[b]	0.122 ± 0.007[b]	0.179 ± 0.008[b]

Values (μmol Pi liberated/min/mg protein) are mean ± SEM of 12 animals per group.
[abc]Values with same superscript are statistically, but not significantly, different at $P < 0.05$.

To evaluate whether alterations in renal cellular functionality in the diabetic animals was caused by dietary modulation, the activities of a few key enzymes of the kidney tissue were quantitated. The levels of enzymes of the polyol pathway (i.e., aldose reductase and sorbitol dehydrogenase) were elevated in the renal tissue of diabetic rats similar to an earlier report.[36] Enhanced metabolism of glucose by the polyol pathway that leads to accumulation of sorbitol and fructose has been found in the tissues in cases of diabetic complications.[37] In our study, diabetic animals exhibited increased LDH and glucose-6-phosphatase (which are responsible for higher gluconeogenesis) and lower glucose-6P-dehydrogenase activity (thus lesser glucose oxidation) when compared with normoglycemic animals. Onion significantly lowered the polyol pathway enzymes in diabetic rats and reversed the changes in enzyme activities of carbohydrate metabolism that occurred due to diabetes. This beneficial effect may have resulted primarily from the hypoglycemic potential of dietary onion in diabetes, which we reported earlier.[13]

Membrane lipids can influence the function of certain membrane proteins such as those involved in the ion transport system.[38] Several ion transport abnormalities have been reported in patients with diabetes mellitus.[39] Na^+, K^+-ATPase, Ca^{++}-ATPase, and Mg^{++}-ATPase form an essential part of plasma membrane and play important roles in the active transport of ions. The significant decreases that were observed in the activities of Na^+, K^+-ATPase, Ca^{++}-ATPase, and Mg^{++}-ATPase under the diabetic conditions in our current study is consistent with the reported decrease in renal Na^+, K^+-ATPase activity in diabetic condition.[39,40] However, Animesh and Ganguli[41] reported an absence of any change in Ca^{2+}- and Mg^{2+}-ATPases in diabetic rat kidney basolateral membranes. The extent of the decreases in kidney ATPases in our study was less in onion-fed diabetic rats. Decreased Na^+, K^+-ATPase activity has been attributed to an inhibitory effect of elevated plasma lysophosphatidylcholine in patients with diabetes.[42] We also observed that dietary onion has a significant phospholipid-lowering effect in diabetic animals, which are characterized by hyperphospholipidemia. Hence, increases in the renal

ATPase activities of diabetic animals that were caused by dietary onion could be due to its hypophospholipidemic effect, which we reported earlier.[13]

Phosphatases and aminotransferases of renal tissue were high in diabetic rats, and dietary onion showed a pronounced reversing trend on this. Aminotransferases are involved in the interconversion of metabolic intermediates relative to energy metabolism and gluconeogenesis.

The salient observations of the current study that dietary onion decreases the leaching of renal tubular enzymes and albuminuria, partially reverses some of the alterations in the activities of kidney cellular enzymes associated with diabetes and of ATPases of renal membranes, and lowers nephromegaly in diabetic animals collectively indicate that dietary onion exerts a beneficial ameliorating influence on the early renal lesions associated with diabetes. This favorable influence of onion on renal lesions in diabetes could probably be attributed to its hypolipidemic and antioxidant effects that we reported earlier[13] analogous to that of curcumin, the active principle of turmeric.[12] Such an effect was not observed here with capsaicin, which is the pungent principle of red pepper, probably because it does not have any significant hypolipidemic or lipid peroxide lowering action in diabetic animals.[13]

Hyperglycemia in diabetes leads to autooxidation of glucose and generation of reactive oxygen species,[43] which are the causes of many diabetic complications. It is known that oxidative DNA damage is increased in the diabetic kidney, suggesting the involvement of oxygen radicals in the process of diabetic nephropathy.[44] In the case of onion feeding, which has a moderate hypoglycemic influence,[13] the possibility that modulation of the hyperglycemic status also contributes to the amelioration of renal lesions cannot be ruled out. The active principles in onion that are responsible not only for the flavor attributes but also for the beneficial physiologic effects are believed to be the sulfur compounds, especially S-methyl cysteine sulfoxide.[45] Recognition of this new therapeutic attribute of dietary onion on a diabetic secondary complication might open a new vista in the dietary management of diabetes mellitus.

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