L-Carnitine Protects Against Cyclosporine-Induced Pancreatic and Renal Injury in Rats


ABSTRACT

Background. L-carnitine has protective effects against various types of injury. This study was designed to evaluate the beneficial effects of L-carnitine on pancreatic and renal injuries caused by cyclosporine (CsA).

Methods. Rats maintained on a low sodium diet were given vehicle (olive oil, 1 mL/kg/d), CsA (15 mg/kg/d), L-carnitine (50 or 200 mg/kg/d), or a combination of CsA and L-carnitine for 4 weeks. The impact of L-carnitine on pancreatic injury was assessed by blood glucose levels, plasma insulin concentrations, and hemoglobulin A1c (HbA1c). In addition, the protective effects of L-carnitine against CsA-induced kidney injury were evaluated in terms of renal function, histopathology (inflammatory cell influx and tubulointerstitial fibrosis), oxidative stress (8-hydroxy 2'-deoxyguanosine, 8-OHdG), transforming growth factor-beta1 (TGF-β1), apoptosis (caspase-3), and autophagy (LC3-II).

Results. CsA treatment caused diabetes, renal dysfunction, tubulointerstitial inflammation (ED-1-positive cells), and fibrosis, which were accompanied by an increase in 8-OHdG production and upregulation of TGF-β1, caspase-3, and LC3-II. Concomitant administration of L-carnitine increased plasma insulin concentrations, decreasing plasma glucose and HbA1c levels. In the kidney, L-carnitine induced dose-dependent improvement of renal function, inflammation, and fibrosis in parallel with suppression of the expression of TGF-β1 and 8-OHdG. Furthermore, the administration of L-carnitine at a high dose inhibited the expression of caspase-3 and LC3-II.

Conclusion. These findings suggest that L-carnitine has a protective effect against CsA-induced pancreatic and renal injuries.

Despite the development of newer immunosuppressants, cyclosporine (CsA) remains a potent immunosuppressive agent that is used for treating multi-organ transplantation and autoimmune diseases. However, the clinical usage of CsA is frequently impeded by its nephrotoxic effects in terms of acute and chronic nephrotoxicity. Acute CsA nephrotoxicity is regarded as being reversible and seems to be caused by a reduction in renal blood flow related to afferent arteriolar vasoconstriction. However, the long-term administration of CsA causes...
progressive renal insufficiency with striped tubulointerstitial fibrosis (TIF), tubular atrophy, inflammatory cell influx, and hyalinosis of the afferent arterioles.\textsuperscript{3,4} The mechanism underlying chronic CsA nephropathy is multifactorial, and several factors, including the intrarenal reninangiotensin system, inflammatory mediators, the transforming growth factor-beta 1 (TGF-\(\beta 1\)), oxidative stress, apoptotic cell death, and excessive autophagy, have been implicated in this condition.\textsuperscript{5,6}

Posttransplant diabetes mellitus (PTDM) is a common and serious complication after kidney transplantation that is associated with decreased graft and patient survival.\textsuperscript{5} A recent meta-analysis of observational studies and randomized controlled trials reported that the incidence of PTDM in the first year after transplantation varied from 2\% to 50\%. The incidence of PTDM is higher in the first 6 months after transplantation.\textsuperscript{7} Although its etiopathogenesis is multifactorial, PTDM is thought to be related to the increased insulin resistance that results from glucocorticoids\textsuperscript{8} and to the decreased insulin secretion caused by calcineurin inhibitors.\textsuperscript{9,10} PTDM results in adverse outcomes, such as decreased graft survival, increased cardiovascular mortality, and increased risk of postoperative infections.\textsuperscript{11}

L-carnitine (\(\beta\)-hydroxy-\(\gamma\)-N-trimethyl ammonium-butyrate) is a component of lipid metabolism that is important for the production of adenosine triphosphate (ATP) through the \(\beta\)-oxidation of long-chain fatty acids. In this manner, L-carnitine functions as an indirect antioxidant and facilitates the repair of oxidized membranes or lipid bilayers.\textsuperscript{12} In addition, L-carnitine activity has also been reported to be a direct scavenger of \(\mathrm{O}_2^-\) and \(\mathrm{H}_2\mathrm{O}_2\).\textsuperscript{13} Thus, L-carnitine may possess antioxidant properties beyond its action on lipid metabolism. It is well known that L-carnitine is necessary for the efflux of acyl groups from mitochondria. Therefore, L-carnitine supplementation is known to play a beneficial role in insulin resistance or diabetic podocyte injury,\textsuperscript{14,15} as intracellular accumulation of acyl-CoA derivatives has been implicated in the development of insulin resistance or diabetic podocyte injury,\textsuperscript{14,15} as intracellular accumulation of acyl-CoA derivatives has been implicated in the development of insulin resistance or diabetic podocyte injury.\textsuperscript{14,15} As such, L-carnitine supplementation is known to play a beneficial role in insulin resistance or diabetic podocyte injury.\textsuperscript{14,15} Nevertheless, the molecular mechanism underlying the benefits of L-carnitine on CsA-induced pancreatic and renal injuries remains unexplored.

In view of the findings described above, the present study was undertaken to evaluate the protective effect of L-carnitine on CsA-induced pancreatic and renal injuries using a well-described rat model of chronic CsA nephropathy.

MATERIALS AND METHODS

Experimental design

The experimental protocol was approved by the Animal Care Committee of the Catholic University of Korea. Male Sprague-Dawley rats (Charles River Technology, Korea), initially weighing 180 to 200 g, were housed in cages (Nalge Co, Rochester, NY, USA) in a controlled-temperature and controlled-light environment and allowed free access to a low salt diet (0.05\% sodium, Teklad Premier, Madison, Wis, USA) throughout the experimental period. A total of 45 rats were randomized into 6 subgroups and treated daily for 4 weeks as follows: (1) vehicle group (VH, \(n = 7\)): rats received olive oil (1 mL/kg/d subcutaneous) (2) VH + L-carnitine group (VH + L50, \(n = 7\)): rats received olive oil and L-carnitine (50 mg/kg intravenously); (3) VH + L-carnitine group (VH + 200, \(n = 7\)): rats received olive oil and L-carnitine (200 mg/kg intravenously); (4) CsA group (C, \(n = 8\)): rats received CsA (15 mg/kg/d subcutaneous); (5) CsA + L-carnitine group (C + L50, \(n = 8\)): rats received CsA and L-carnitine (50 mg/kg intravenously); (6) CsA + L-carnitine group (C + L200, \(n = 8\)): rats received CsA and L-carnitine (200 mg/kg intravenously). The dosage and method of CsA\textsuperscript{2} and L-carnitine administration\textsuperscript{20,21} were chosen based on previous reports.

Animals were euthanized under ketamine anesthesia, and blood and the kidney samples were collected for biochemical and morphologic or molecular examinations.

Basic Parameters

Rats were pair-fed and daily body weight (BW) was monitored. Before sacrifice, rats were individually housed in metabolic cages (Tecniplast Gazzada S. a r.l., Italy) for 24 hour urine collection, and blood samples were withdrawn to evaluate serum creatinine (SCR), blood urea nitrogen (BUN), blood glucose levels, and plasma insulin level (Coulter-STKS; Coulter Electronics). An intraperitoneal glucose tolerance test (IPGTT) was performed at the end of the 4-week treatment period as previously described,\textsuperscript{22} and the area under the curve of glucose (AUCg) was calculated by trapezoidal estimation from the values obtained in the IPGTT. Whole blood CsA level was measured by a monoclonal radioimmunoassay (Incasto Co, Stillwater, Minn, USA).

Histopathology

Harvested rat kidney tissues were fixed in periodate-lysine-paraformaldehyde solution and embedded in wax. After dewaxing, 4 \(\mu\)m sections were processed and stained with Masson trichrome and hematoxylin. A finding of TIF was defined as a matrix-rich expansion of the interstitium with tubular dilatation, tubular atrophy, tubular cast formation, sloughing of tubular epithelial cells, or thickening of the tubular basement membrane. A minimum of 20 fields per section was assessed using a color image analyzer (TDI Scope Eye Version 3.0 for Windows, Olympus, Japan). Briefly, the images were captured, and the extent of TIF was quantified using the Polygon program by counting the percentage of areas injured per field of cortex under 100 \(\times\) magnification. Histopathologic analysis was performed in randomly selected cortical fields of sections by a pathologist blinded to the identity of the treatment groups.

Enzyme-Linked Immunosorbent assay

Twenty-four-hour urinary concentrations of the DNA adduct 8-hydroxy-2'-deoxyguanosine (8-OHdG) were determined using a competitive enzyme-linked immunosorbent assay (Japan Institute for the Control of Aging, Shizouka, Japan), according to the manufacturer’s protocol. All samples were assayed in triplicate.
Immunohistochemistry

After dewaxing, sections were incubated with a 0.5% Triton X100-phosphate-buffered saline (PBS) solution for 30 minutes and washed with PBS three times. Nonspecific binding sites were blocked for 1 hour with normal donkey serum diluted 1:10 in PBS, and then incubated overnight at 4°C with anti-8-OHdG monoclonal antibody (JaIgA, Shizouka, Japan) diluted in 1:1000 in a humid environment. After rinsing in Tris-buffered saline (TBS), sections were incubated in peroxidase-conjugated donkey anti-mouse or rabbit IgG Fab fragment (Jackson Immuno Research Laboratories, West Grove, Pa, USA) for 30 minutes. For staining, sections were incubated with a mixture of 0.05% 3,3-diaminobenzidine containing 0.01% H2O2 at room temperature until a brown color was visible, washed with TBS, counterstained with hematoxylin, and examined under light microscopy. The procedure of immunostaining for TGF-β1 (1:500, Santa Cruz Biotechnology, Inc) and ED-1 (1:500, Serotec, Inc, UK) was similar to that for 8-OHdG. Semiquantitative analyses of TGF-β1 and ED-1 expression were performed using a color image autoanalyzer (TDI Scope Eye Version 3.5 for Windows; Olympus, Japan) by counting the percentage of stained areas per field of cortex at 100× magnification. A minimum of 20 fields per section were counted and averaged.

Western Blotting

Kidney cortex tissue was homogenized in lysis buffer (20 mmol/L Tris-Cl [pH 7.6], 150 mmol/L NaCl, 1% [wt/vol] sodium deoxycholate, 1% [vol/vol] Triton X-100, 0.1% sodium dodecyl sulfate, 2 mmol/L NaVO3, and freshly added 1% [vol/vol] aprotonin, leupeptin [1 μg/mL], pepstatin [1 μg/mL], and 1 mmol/L phenylmethyl sulfonyl-fluoride). Homogenates were centrifuged at 3000 rpm for 15 minutes at 4°C, and the protein concentration of the lysate was determined using a protein microassay of the Bradford method (Bio-RAD, Hercules, California, USA). Protein samples were resolved on 15% SDS-polyacrylamide gel electrophoresis and then electroblotted onto Bio-Blot nitrocellulose membrane (Bio-RAD). An equal amount of protein loading (80 μg) was verified by Ponceau S staining. The membrane was blocked for 1 hour in TBS added Tween-20 (TBS-T, 10 mmol/Tri-CL, 150 mmol/L NaCl [pH 8.0], 0.05% Tween-20) containing 5% nonfat powdered milk. Anti-caspase-3, active form (1:200; Millipore Corporation, Calif, USA) or microtubule-associated protein 1 light chain 3 phospholipid-conjugated form (LC3-II, 1:1000; Sigma-Aldrich, USA) was detected by incubating for 1 hour with specific primary antibodies. Primary antibody incubation was followed by 6 washes of TBS-T. The blot was then incubated with secondary antibody (Donkey anti-rat IgG, horseradish peroxidase) conjugate at 1:2000 (Amer sham Biosciences, UK) for 1 hour. Antibody-reactive protein was detected using enhanced chemiluminescence (Amer sham Biosciences, UK). Optical densities were obtained using the VH group as 100% reference and normalized with β-actin.

Statistical Analysis

Data are expressed as mean ± standard error of the mean unless otherwise specified. Multiple comparisons among groups were performed by one-way analysis of variance with the post hoc Bonferroni test (SPSS software version 19.0, Microsoft Corp, Chicago, Ill, USA). Statistical significance was assumed as P < .05.

RESULTS

Effect of L-Carnitine on Basic Parameters in Chronic CsA Nephropathy

CsA-treated rats exhibited weight loss (weight gain: 75.6 ± 2.6 vs 89.9 ± 2.4, P < .01) and decreased renal function (SCr, 0.55 ± 0.02 mg/dL vs 0.42 ± 0.03 mg/dL, P < .01; BUN, 29.4 ± 0.94 mg/dL vs 11.3 ± 0.48 mg/dL, P < .01) compared with VH-treated rats. However, BW was increased (weight gain: 85.3 ± 3.0 vs CsA, P < .05) and renal function was improved after L-carnitine coadministration compared with the CsA group (SCr, 0.48 ± 0.02 mg/dL vs CsA, P < .05; BUN, 27.4 ± 1.02 mg/dL vs CsA, P < .05). Whole blood CsA concentration was unaffected by the combination of L-carnitine and CsA, as shown in Table 1.

Effect of L-Carnitine on CsA-Induced Diabetes

Baseline blood glucose concentration did not differ between the 6 groups (Fig 1A). IPGTT was significantly increased in the CsA group compared with the VH group, whereas the CsA + L group showed a significant decrease in IPGTT compared with the CsA group (Fig 1A). The calculated AUCg did not differ significantly between the VH and VH + L groups and was lower in the CsA + L group than it was in the CsA group (L50: 476.2 ± 14.6 mg/dL minutes vs 44.11 ± 12.6 mg/dL minutes, P < .05; L200: 476.2 ± 14.6 mg/dL minutes vs 396.9 ± 9.6 mg/dL minutes, P < .05; Fig 1B). Serum insulin level did not differ significantly between the VH and VH + L groups. However, serum insulin concentration in the CsA group was significantly lower than that observed in the VH (5.1 ± 0.8 mg/dL minutes vs and 1.1 ± 0.3 mg/dL minutes, P < .05) and VH + L group (L50: 5.1 ± 1.0 mg/dL minutes vs CsA, P < .05; L200: 4.8 ± 0.4 mg/dL minutes vs CsA, P < .05), and was significantly higher in the

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WG, weight gain (g); UV, urine volume (mL/d); SCr, serum creatinine (mg/dL); BUN, blood urea nitrogen (mg/dL); CsA con, CsA concentration (ng/mL); TIF, tubulointerstitial fibrosis (%0.5/mm²); CsA, Cyclosporine; VH, vehicle group; L, L-carnitine.

• P < .05 vs VH.
• P < .05 vs CsA.
• P < .05 vs CsA + L50.
CsA + L group compared with the CsA group (L50: 2.7 ± 0.5 mg/dL minutes vs CsA, \( P < .05 \); L200: 2.8 ± 0.2 mg/dL minutes vs CsA, respectively; Fig 1C).

Effect of L-Carnitine on Macrophage Infiltration and Fibrosis in Chronic CsA Nephropathy

ED-1-positive cells were detected only rarely in the kidneys of VH-treated animals. CsA treatment increased the number of ED-1-positive cells (29 ± 1.0/0.5 mm\(^2\) vs 5 ± 0.7/0.5 mm\(^2\), \( P < .01 \)). Concomitant administration of L-carnitine significantly decreased the number of ED-1-positive cells (23 ± 1.2/0.5 mm\(^2\) vs CsA, \( P < .01 \)), which was more pronounced after the administration of 200 mg/kg L-carnitine compared with the CsA + L50 group (Fig 2, 19 ± 2.0/0.5 mm\(^2\) vs CsA + L50, \( P < .05 \)).

CsA-treated rats exhibited the typical striped TIF of chronic CsA nephropathy (Table 1). A significant increase in the percentage of TIF was found in the CsA group compared with the VH group (34.1% ± 3.2%/0.5 mm\(^2\) vs 0% ± 0%/0.5 mm\(^2\), \( P < .01 \)). In contrast, the percentage of TIF decreased markedly when L-carnitine was coadministered (28.7% ± 3.6%/0.5 mm\(^2\) vs CsA, \( P < .05 \)) and a further decrease was observed in the CsA + L200 group (23.8 ± 2.5%/0.5 mm\(^2\) vs CsA + L50, \( P < .05 \)).

Effect of L-Carnitine on TGF-\( \beta \) Expression in Chronic CsA Nephropathy

Immunohistochemistry revealed that the majority of VH-treated rat kidneys were negative for TGF-\( \beta \)1. In contrast, the expression of the TGF-\( \beta \)1 protein was dramatically increased in the tubulointerstitium in CsA-treated rat kidneys (46.0% ± 2.3%/0.5 mm\(^2\) vs 17.1% ± 0.5%/0.5 mm\(^2\), \( P < .01 \)). It is notable that the sites of strong TGF-\( \beta \)1 protein expression were located in areas of inflammatory cell infiltration and severe TIF (Fig 3A). L-carnitine suppressed TGF-\( \beta \)1 protein expression in a dose-dependent manner (CsA + L50: 40.0% ± 1.4%/0.5 mm\(^2\), \( P < .05 \) vs CsA; CsA + L200: 30.2% ± 3.0%/0.5 mm\(^2\), \( P < .05 \) vs CsA + L50, respectively; Fig 3B).

Effect of L-Carnitine on Oxidative Stress in Chronic CsA Nephropathy

Chronic CsA nephropathy is closely associated with oxidative stress. As shown in Fig 4, immunohistochemistry showed a significant increase in 8-OHdG expression and

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**Fig 1.** Effect of L-carnitine (L) on diabetic biomarkers. (A) Blood glucose levels (intraperitoneal glucose tolerance test [IPGTT]). (B) Calculation of area under the curve of glucose (AUCg). (C) Plasma insulin levels. Note that cyclosporine (CsA) induced an elevation in blood glucose and HbA1c and a decrease in plasma insulin levels, whereas coadministration of L reversed all of these parameters. \(^\# P < .01 \) vs vehicle group of (VH); \(^{##} P < .05 \) vs CsA.
immunoreactivity in CsA-treated rat kidneys; these signals were confined to cortical tubular epithelial cells. Interestingly, the sites of strong 8-OHdG expression were located in areas of injured or atrophied tubules (Fig 4A). Concomitant administration of L-carnitine significantly decreased intrarenal 8-OHdG expression compared with the CsA treatment alone. Moreover, this decrease was more pronounced in the presence of a higher dose of L-carnitine compared with the CsA + L50 group. In parallel, urinary 8-OHdG excretion in the CsA-treated group was higher than that observed in the VH-treated group (241.0 ± 37.2 ng/d vs 130.7 ± 17.0 ng/d, \( P < .01 \)), whereas its level was significantly decreased after concomitant administration of L-carnitine, in a dose-dependent manner (Fig 4B, CsA + L50: 208.3 ± 19.7 ng/d vs CsA, \( P < .05 \); CsA + L200: 177.2 ± 12.7 ng/d vs CsA + L50, \( P < .05 \), respectively).

### Effect of L-Carnitine on LC3-II and Caspase-3 in Chronic CsA Nephropathy

The presence of autophagy was measured based on LC3-II, whereas apoptosis was assessed based on the detection of the apoptosis-related caspase-3 protein, using Western blotting. The results showed that CsA treatment upregulated LC3-II (183% ± 11% vs 102% ± 6%, \( P < .01 \)) and...
caspase-3 (169% ± 13% vs 103% ± 2%, P < .01) compared with the VH group. Concomitant administration of L-carnitine at a dose of 200 mg/kg inhibited the expression of LC3-II (Fig 5A and Fig 5B, 133% ± 10% vs CsA, P < .05 and caspase-3 (Fig 5A and Fig 5C, 124% ± 12% vs CsA, P < .05) expression.

DISCUSSION
The results of the present study demonstrate clearly that L-carnitine offers a protective effect against CsA-induced pancreatic and renal injuries in a rat model of chronic CsA nephropathy. The renoprotective effect of L-carnitine against CsA-induced renal injury was illustrated by its inhibition of tubulointerstitial inflammation and fibrosis, apoptosis, and autophagy. In the pancreas, L-carnitine treatment decreased CsA-induced diabetic control values. Our findings may provide a potential rationale for the clinical use of L-carnitine to reduce CsA-induced nephropathy and diabetes.

The main pathogenesis of CsA-induced diabetes is caused by the direct toxicity of CsA on pancreatic β cells, which leads to a decrease in insulin secretion and synthesis; in contrast, insulin resistance plays a minor role in this phenomenon. We demonstrated previously that CsA treatment induces a dramatic reduction in pancreatic islet size, insulin immunoreactivity, and vacuolization of islet cells. As a result, the present study measured blood diabetic controls. The results of this study revealed that CsA
treatment led to a significant elevation in blood glucose, which was accompanied by a decrease in plasma insulin and increase in hemoglobin A1c (HbA1c). The concomitant administration of L-carnitine reversed all of the biomarkers. These findings suggest that L-carnitine may counteract CsA-induced toxicity in the pancreas. Our results are consistent with those reported by studies performed using human and animal samples, which revealed that L-carnitine reverses blood glucose levels, insulin resistance, and HbA1c levels.

The mechanism via which L-carnitine improved pancreatic function in this model is unknown; however, 2 possibilities should be considered. First, chronic CsA treatment induces oxidative stress injury, which ultimately leads to the apoptosis of pancreatic β cells induced by low-density lipoprotein. L-carnitine ameliorates pancreatic myeloperoxidase and glutathione-S-transferase enzymatic activities in caerulein-induced acute pancreatitis via an antioxidant effect. Second, mitochondrial dysfunction plays a central role in ATP synthesis and content in β cells, which regulates glucose-stimulated insulin secretion. Studies performed in vivo and in vitro have confirmed that L-carnitine improves the mitochondrial membrane potential and upregulates uncoupling protein-2, thus preventing mitochondrial dysfunction in β cells. Based on our data regarding blood glucose levels and previous reports, we propose that the benefits of L-carnitine on pancreatic β cells may be associated with its action on mitochondrial and oxidative stress.

The most notable finding of our study was that L-carnitine treatment suppressed inflammation and TIF in chronic CsA nephropathy. As reported previously by our group and others, inflammation and TIF induced by CsA are the typical pathologic features of chronic CsA nephropathy. Moreover, the anti-inflammatory and anti-fibrotic effects of L-carnitine have been observed in isolated rat kidneys from a rat model of this condition. However, the molecular mechanism underlying the renoprotection afforded by L-carnitine remains unknown. Therefore, this study assessed the effect of L-carnitine on macrophage influx and profibrotic TGF-β1. We found that L-carnitine significantly decreased the number of ED-1-positive cells and TGF-β1 expression in a dose-dependent manner, which was accompanied by a marked attenuation of TIF. Our results suggest that L-carnitine inhibits the development of tubulointerstitial inflammation and fibrosis in chronic CsA nephropathy via a mechanism involving suppressed macrophage influx and TGF-β1 expression.

It is well accepted that oxidative stress plays a pivotal role in the pathogenesis of chronic CsA nephropathy. In addition, overwhelming evidence suggests that CsA treatment induces oxidative stress injury via the production of reactive oxygen species and malondialdehyde and downregulation of antioxidant enzymes, such as superoxide dismutase and glutathione peroxidase. This concept is supported by studies demonstrating that antioxidant treatment significantly ameliorates chronic CsA-induced renal injury. L-carnitine, which is a potential antioxidant agent, has been shown to protect against various types of nephrotoxicity in vivo and in vitro via its antioxidant properties. In this study, we found that L-carnitine decreased intrarenal 8-OHdG expression and urinary production. The suppression of oxidative stress occurred in parallel with a significant improvement of renal function, as well as TIF. Our findings are supported by the results of previous studies and suggest that the renoprotective role of L-carnitine observed in this study may be related, in part, to the inhibition of 8-OHdG.

L-carnitine protects against renal ischemia-reperfusion injuries; in addition, its antiapoptotic effect is regarded as a protective mechanism against ischemic injury. More recently, we have shown that renal cell apoptosis and excessive autophagy are closely associated with the development of tubulointerstitial injury in chronic CsA nephropathy. In the present study, we chose to compare 2 doses of L-carnitine (50 and 200 mg/kg). Interestingly, the lower dose of L-carnitine did not influence apoptosis (active caspase-3) and autophagy (LC3-II), whereas the higher dose of L-carnitine improved not only pathologic damage, but also apoptosis and autophagy. These observations suggest that, although a low dose of L-carnitine (50 mg/kg) failed to overcome the hemodynamic changes caused by CsA, this compound was effective in preventing the development of chronic CsA-induced nephropathy.

In summary, CsA-induced diabetes and renal injury are common clinical dilemmas in the transplantation field. Our results provide a rationale for the use of the non-nephrotoxic agent L-carnitine in the management of diabetes in transplant recipients taking CsA.

REFERENCES


