Renal Changes Associated With Cyclosporine in Recent Type I Diabetes Mellitus

Michel Rodier, Jean Ribstein, Claire Parer-Richard, and Albert Mimran

The effects of cyclosporine A treatment on arterial pressure and renal function were assessed in 11 young patients with type I diabetes of short duration. Cyclosporine was started at 7.5 mg/kg/day, progressively decreased to 6.3 mg/kg/day at 6 months, and then continued at a lower dose (4.1 mg/kg/day) for an additional 3 months in patients in whom remission of insulin dependency was obtained (n=6). After 3 months of cyclosporine, a slight but significant increase in arterial pressure (+5.2±1.5 mm Hg), a rise in renal vascular resistance (~20%), a decrease in glomerular filtration rate (~25%), and a fall in filtration fraction were observed. Such changes were sustained after 6 and eventually 9 months of therapy. The decrease in glomerular filtration rate observed during cyclosporine treatment contrasted with the lack of change in simultaneously estimated creatinine clearance; in fact, the creatinine clearance/glomerular filtration ratio increased from 1.07±0.05% to 1.33±0.09% within 3 months of cyclosporine therapy, thus suggesting an enhanced tubular secretion of creatinine. Plasma renin activity and urinary excretion of kallikrein decreased significantly (~50%), whereas plasma aldosterone concentration remained unaltered and plasma concentration of potassium increased during cyclosporine therapy. These changes were observed in the presence of a constant urinary excretion of sodium and potassium and a constant body weight. All parameters returned to pretreatment values within 3 months after cessation of cyclosporine. These results indicate that cyclosporine given for 6–9 months at a moderate dose causes a deleterious but reversible effect on arterial pressure and renal function in young diabetic patients. (Hypertension 1991;18:334–340)

Several multicenter trials have demonstrated that cyclosporine A (CsA) treatment started early after the clinically apparent onset of type I diabetes mellitus is associated with a significant increase in the incidence and duration of remission from insulin dependency.1,2 Nevertheless, the sustained benefits of CsA treatment are not clearly established. In most studies performed in recipients of renal3 or cardiac4 transplants, as well as in patients with autoimmune diseases such as uveitis,5 rheumatoid arthritis,6 psoriasis,7 or primary biliary cirrhosis,8 a significant impairment in renal function and an increase in arterial pressure were observed during short-term9 and long-term10 CsA therapy. In contrast with these results, no modification of renal function, as assessed by chromium-labeled ethylenediaminetetraacetic acid clearance, was reported in diabetic children receiving CsA.10 Reversibility of CsA-associated renal dysfunction after reduction or discontinuation of therapy is not a constant finding.9,11

The present studies were performed in patients with type I diabetes of recent onset to assess the changes in renal function associated with a moderate dosage of CsA and to evaluate its eventual reversibility after cessation of the immunosuppressive agent. Such an evaluation of renal parameters was considered important in view of the known frequent involvement of the kidney during the evolution of diabetes mellitus.12

Methods

Patients

The study population consisted of 11 patients aged 15–40 years with type I diabetes mellitus diagnosed according to World Health Organization criteria.13 Subjects were symptomatic for less than 3 months (range 3–12 weeks) and were treated with insulin for less than 2 months (range 1–8 weeks). Exclusion criteria are detailed in a previous report.1 Eligible patients received oral and written information, and individual written consent was obtained before their inclusion in the study. Of note, none of these subjects had a positive history of hypertension, defined as one
Methods

Treatments. Patients were first evaluated after 1 week of optimal metabolic control (basal period) and after 3 and 6 months of CsA therapy. CsA was given once daily (before breakfast), and the starting dose was 7.5 mg/kg/day. CsA dosage was then adapted to maintain a whole-blood trough level of 300–500 ng/ml (radioimmunoassay technique using a polyclonal antibody); however, maximum CsA dosage never exceeded 10 mg/kg/day. After a 5-month period of CsA treatment at full dose, the dosage was reduced by 20% every 10 days to obtain trough levels between 100 and 200 ng/ml. In case of remission of insulin dependency, either complete (defined as a good metabolic control, that is, fasting blood glucose less than 7.8 mmol/l and glycosylated hemoglobin 7.5% or less, without insulin) or partial (good metabolic control with less than 0.25 units/kg/day insulin), CsA treatment was maintained up to the ninth month when renal function was reevaluated. When no significant remission was observed within 6 months, treatment was discontinued. In all patients, a final evaluation was performed 3 months after CsA withdrawal.

Patients were initially treated by insulin three times a day and trained in glucose self-monitoring. At least 15 capillary blood glucose measurements were obtained weekly, and insulin was adapted daily to reach near-normal glycemic level. Metabolic control was assessed by monthly determinations of glycosylated hemoglobin Aj (chromatographic method, normal values of less than 5.8%).

Study protocol. Each evaluation of renal function was performed over 3 consecutive days. Renal clearance studies were performed on the first day using a protocol previously described. Briefly, after their usual breakfast and administration of the morning dose of insulin, patients came to the hospital at 8:00 AM with the total urine collection of the preceding 24 hours. To obtain a consistent diuresis, a water load of 10 ml/kg body weight was given on arrival, and intravenous catheters were placed in both forearms. Priming doses of [131I]-sodium orthiiodohippurate (for the measurement of effective renal plasma flow [ERPF]) and [99mTc]-diethylene pentatetraacetate acid (for the estimation of glomerular filtration rate [GFR]) were injected. A continuous infusion of both markers dissolved in a 0.45% NaCl solution was then given at a rate of 4 ml/min. After a 1-hour equilibration period, the bladder was emptied by spontaneous voiding, and three to four 20–30 minute urine collections were obtained. At the end of each urine collection, patients drank a volume of water equal to the preceding urine volume. Blood samples were drawn at midpoint of each clearance period. Arterial pressure and heart rate were continuously monitored using an automatic device (Dynamap 845, Critikon, Créteil, France). The effect of a standardized exercise on the urinary excretion of albumin was assessed on a separate day, as previously reported. On the final day, renal concentrating capacity after intranasal administration of 40 μg desmopressin was evaluated.

Analytical methods. Whole-blood trough levels of CsA were estimated using a polyclonal antibody (Sandoz polyclonal antibody kit, Basel, Switzerland). Concentrations of creatinine and electrolytes were measured in all plasma and urine samples. Urinary albumin was estimated on 24-hour urine collections and on samples obtained during clearance studies, at rest, and after exercise, using a nephelometric method (Behring, Marburg, FRG). β2-Microglobulin was estimated on 24-hour urine collections by radioimmunoassay (Phadebas Pharmacia, Uppsala, Sweden). Supine plasma renin activity and plasma aldosterone concentration were measured using radioimmunoassay techniques (CEA-Sorin kit, Saclay, France). Urinary kallikrein activity was determined by the amidolytic method using the synthetic substrate p. nitroanilide (Kabi, Stockholm, Sweden).

Results

Parameters Related to Diabetes Control

At entry into the study, patient mean body mass index was 19.8±0.6 kg/m². Glycosylated hemoglobin was elevated (11.6±0.8%); however, concomitant blood glucose was in the near-normal range (7.4±1.3 mmol/l). As summarized in Table 1, metabolic control assessed by the measurement of glycosylated hemoglobin was improved during CsA therapy, and insulin requirements were markedly reduced. Of interest, blood glucose levels were similar at the time of each renal function study.

After 3 months of CsA therapy, seven of 11 patients experienced total (n=3) or partial (n=4) remission of insulin dependency. At 6 months, only six patients remained in remission and were thus maintained on immunosuppressive therapy for an additional 3-month period; CsA was discontinued in the remaining five patients. Within 3 months of CsA withdrawal, insulin dependency had reappeared in all patients; however, the insulin dosage was significantly lower than at entry into the study.

CsA level was within the goal range at 3 months (401±45 ng/ml) and was only slightly lower at 6 months (308±49 ng/ml) despite a significant reduction in dosage. In the six patients maintained on a lower CsA dose (4.1±0.4 mg/kg/day) for an additional 3-month period, CsA level decreased to 199±26 ng/ml.

Influence of Cyclosporine on Arterial Pressure and Renal Function

Arterial pressure before CsA administration was normal in all patients (range 111–126/55–79 mm Hg). As shown in Table 2 and Figure 1, arterial pressure

or both parents with high blood pressure or treated with antihypertensive therapy.
slightly increased in response to CsA therapy. This increase was consistent at 3 months (+5.2±1.5 mm Hg for mean arterial pressure) and remained at the same level thereafter in patients treated for 6 (n=11) or 9 (n=6) months. A rise in diastolic arterial pressure of more than 10 mm Hg was observed in 5 of 11 patients; however, arterial pressure did not reach a hypertensive level (defined as a diastolic arterial pressure higher than 90 mm Hg) in any of the patients. The increase in arterial pressure was not associated with any change in body weight or hematocrit and occurred in the presence of an unchanged sodium intake, as suggested by the similar value of 24-hour urinary sodium excretion found at all stages of the study (Table 3).

At entry into the study, GFR (range 102-164 ml/min/1.73 m²) was within normal limits with respect to age, as assessed in our laboratory, in eight patients and clearly exceeded expected values in the remaining three. As depicted in Table 2 and Figure 2, a sustained and consistent decrease in GFR occurred in response to CsA therapy. Surprisingly, no significant change in the simultaneously estimated creatinine clearance was observed, and the creatinine clearance/GFR ratio, which was close to unity before CsA (1.07±0.05), increased during drug treatment (1.33±0.09 and 1.41±0.08 at 3 and 6 months, respectively, both p<0.05).

Before CsA, ERPF ranged between 448 and 828 ml/min/1.73 m². No significant alteration in ERPF occurred during treatment; however, a sustained increase in calculated renal vascular resistance was observed (Figure 2). As a consequence of the disproportionate changes in GFR and ERPF, CsA treatment was associated with a fall in filtration fraction (Table 2).

Effect of Cyclosporine on Renin-Angiotensin System and Urinary Kallikrein Excretion

As summarized in Table 3, CsA treatment resulted in a marked fall in PRA; nevertheless, plasma aldosterone concentration was unchanged. The reduction in PRA occurred in the presence of an unchanged value of 24-hour urinary sodium excretion. In addition, serum potassium increased during CsA, whereas 24-hour urinary potassium excretion was unaltered. As shown in Figure 3, CsA treatment was associated with a 60% decrease in urinary kallikrein excretion.

No correlation was found between changes in renal function or hemodynamics and changes in arterial pressure.

TABLE 1. Effect of Cyclosporine A Therapy on Metabolic Control of Diabetes

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Baseline</th>
<th>CsA treatment</th>
<th>CsA withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (kg)</td>
<td>60.9±2.3</td>
<td>62.9±1.9</td>
<td>63.5±1.7</td>
</tr>
<tr>
<td>Blood glucose (mmol/l)</td>
<td>7.4±1.3</td>
<td>8.5±0.9</td>
<td>7.3±1.3</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>11.6±0.8</td>
<td>7.2±0.3*</td>
<td>8.0±0.5*</td>
</tr>
<tr>
<td>Insulin (units/kg/day)</td>
<td>0.74±0.10</td>
<td>0.25±0.08*</td>
<td>0.42±0.05*</td>
</tr>
<tr>
<td>CsA dose (mg/kg/day)</td>
<td>...</td>
<td>7.2±0.5</td>
<td>...</td>
</tr>
<tr>
<td>Blood trough level (ng/ml)</td>
<td>...</td>
<td>401±45</td>
<td>...</td>
</tr>
</tbody>
</table>

Values are mean±SEM. Blood glucose values were taken at the time of renal studies. CsA, cyclosporine A; HbA1c, glycosylated hemoglobin.

*p<0.05 vs. baseline.

TABLE 2. Effect of Cyclosporine A Therapy on Arterial Pressure and Renal Hemodynamics and Function

<table>
<thead>
<tr>
<th>Measurements</th>
<th>Baseline</th>
<th>CsA treatment</th>
<th>CsA withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAP (mm Hg)</td>
<td>117±2</td>
<td>122±2*</td>
<td>117±2</td>
</tr>
<tr>
<td>DAP (mm Hg)</td>
<td>65±2</td>
<td>71±3*</td>
<td>65±3</td>
</tr>
<tr>
<td>DAP (mm Hg)</td>
<td>82±2</td>
<td>87±2*</td>
<td>82±2</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>65±3</td>
<td>63±5</td>
<td>59±4</td>
</tr>
<tr>
<td>Serum creatinine (µmol/l)</td>
<td>89±5</td>
<td>103±3*</td>
<td>90±3</td>
</tr>
<tr>
<td>Creatinine clearance (ml/min/1.73 m²)</td>
<td>132±9</td>
<td>128±7</td>
<td>135±6</td>
</tr>
<tr>
<td>GFR (ml/min/1.73 m²)</td>
<td>124±6</td>
<td>98±5*</td>
<td>119±5</td>
</tr>
<tr>
<td>Creatinine clearance/GFR ratio</td>
<td>1.07±0.05</td>
<td>1.33±0.09*</td>
<td>1.15±0.07</td>
</tr>
<tr>
<td>ERPF (ml/min/1.73 m²)</td>
<td>614±37</td>
<td>544±27</td>
<td>551±24</td>
</tr>
<tr>
<td>RVR</td>
<td>0.083±0.006</td>
<td>0.101±0.006*</td>
<td>0.087±0.005</td>
</tr>
<tr>
<td>FF (%)</td>
<td>20.5±0.9</td>
<td>18.2±1.3*</td>
<td>21.5±1.0</td>
</tr>
</tbody>
</table>

Values are mean±SEM. CsA, cyclosporine A; SAP, systolic arterial pressure; DAP, diastolic arterial pressure; MAP, mean arterial pressure; GFR, glomerular filtration rate (¹²⁵I-Tc-diethylene pentaacetic acid clearance); ERPF, effective renal plasma flow (¹³¹I-hippuran clearance); RVR, renal vascular resistance calculated as MAP/renal blood flow; FF, filtration fraction.

*p<0.05 vs. baseline.
pressure or urinary kallikrein excretion observed during CsA therapy.

**Effect of Cyclosporine on Urinary Excretion of Proteins**

As shown in Table 4, CsA treatment had no significant influence on the urinary excretion of albumin when measured with the patient in the supine position before and during exercise and during the water load procedure associated with clearance determinations. Urinary excretion of β2-microglobulin was not modified by treatment.

No impairment in the renal concentrating ability of the kidney in response to desmopressin was detected during CsA therapy.

No clear difference was observed between changes at 6 and 9 months of therapy in the six patients maintained on therapy. No influence of the length of CsA administration (6 versus 9 months) on arterial pressure and renal parameters could be detected.

**TABLE 3. Effect of Cyclosporine A Therapy on Electrolytes and Hormonal Parameters**

<table>
<thead>
<tr>
<th>Measurements</th>
<th>Baseline</th>
<th>CsA Treatment</th>
<th>CsA withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>3 months</td>
<td>6 months</td>
</tr>
<tr>
<td>Serum sodium (mmol/l)</td>
<td>140±1</td>
<td>139±1</td>
<td>138±1</td>
</tr>
<tr>
<td>Urinary sodium (mmol/24 hr)</td>
<td>129±34</td>
<td>146±26</td>
<td>156±23</td>
</tr>
<tr>
<td>Serum potassium (mmol/l)</td>
<td>3.72±0.16</td>
<td>4.18±0.12*</td>
<td>4.11±0.05*</td>
</tr>
<tr>
<td>Urinary potassium (mmol/24 hr)</td>
<td>58.7±14.2</td>
<td>61.9±12</td>
<td>60.2±8.6</td>
</tr>
<tr>
<td>Plasma renin activity (ng/ml/hr)</td>
<td>3.2±0.7</td>
<td>1.4±0.3*</td>
<td>0.9±0.2*</td>
</tr>
<tr>
<td>Plasma aldosterone (ng/dl)</td>
<td>12±1.6</td>
<td>9.3±0.9</td>
<td>10.4±1.0</td>
</tr>
</tbody>
</table>

Values are mean±SEM. CsA, cyclosporine A.

*p<0.05 vs. baseline.

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**FIGURE 2.** Bar graphs show percent changes in glomerular filtration rate (GFR), effective renal plasma flow (ERPF), filtration fraction (FF), and renal vascular resistance (RVR) associated with cyclosporine treatment. *p<0.05 as compared with baseline.
Influence of Cyclosporine Withdrawal on Arterial Pressure and Renal Function

After a 3-month period of CsA withdrawal, arterial pressure and GFR as well as renal resistance and hormonal parameters returned to values not significantly different from baseline (Tables 3 and 4). In addition, the creatinine clearance/GFR ratio also decreased toward its initial value (1.15±0.07). These findings clearly demonstrate the reversibility of changes in arterial pressure and renal function associated with CsA treatment.

Discussion

In the present study conducted in young patients with insulin-dependent diabetes mellitus of recent onset, it was shown that CsA treatment, at doses yielding relatively low blood concentrations, was associated with a slight rise in arterial pressure (no patient became hypertensive during treatment) and a moderate and sustained decline in GFR. In addition, CsA administration resulted in a decrease in filtration fraction and a rise in renal vascular resistance, although ERPF was not significantly altered. Such changes in renal function were associated with a consistent depression in the circulating renin level as changes in arterial pressure and renal function associated with CsA treatment.

As observed in previous reports,1,2,10 CsA treatment was associated with a high incidence of remission from insulin dependency. However, insulin therapy had to be reintroduced within 3 months after cessation of CsA in all patients. Of importance, regarding the known influence of hyperglycemia on renal function,18 good diabetic control was achieved at all steps of the investigation.

Hypertension is a rather frequent complication of CsA therapy in recipients of renal as well as cardiac or bone marrow transplantation19 and in patients with autoimmune diseases.5,6,20,21 An increase in diastolic arterial pressure to values above 95 mm Hg was observed in 39% of 72 patients with rheumatoid arthritis, despite a 50% reduction in CsA dosage (mean 3.8 mg/kg/day) when compared with previous studies.21 In 93 insulin-dependent diabetics with a mean age similar to that of our population and in whom CsA was initiated at a dose of 10 mg/kg/day, a 32% incidence of hypertension was found.2 In contrast, hypertension did not develop in a cohort of 40 children with recent insulin-dependent diabetes treated by CsA given at a starting dose of 7.5 mg/kg/day.10 The present study showed that although arterial pressure significantly increased during CsA, it never reached hypertensive values. These observations suggest that increasing age may be a critical factor in the susceptibility of arterial pressure to chronic CsA.

During CsA treatment, a sustained fall in GFR by approximately 25% occurred in the presence of an unchanged renal plasma flow; this resulted in a fall in filtration fraction. In fact, due to the rise in arterial pressure, renal resistance actually increased during treatment. These early changes in renal function associated with CsA may be the consequence of a predominant preglomerular (afferent) vasoconstriction, as suggested by the fall in filtration fraction. Such a proposal is in agreement with experimental observations made in rats treated acutely with CsA by using micropuncture22-24 as well as perfusion cast25 techniques, and showing the occurrence of a predominant rise in afferent arteriolar resistance and a decrease in intraglomerular capillary pressure in response to CsA.22-24 The possibility remains that CsA induces a decrease in the glomerular ultrafiltration coefficient in humans, since such an effect was demonstrated in acutely treated rats.22 The present finding of a lack of decrease in renal plasma flow during CsA therapy may not reflect true changes in renal blood flow since no measurement of the renal extraction of ortho-iodohippurate was performed. Myers et al4 observed that para-aminohippurate extraction was lower in CsA-treated when compared with azathioprine-treated heart transplant recipients with moderate-to-severe impairment in renal function. If such a phenomenon had occurred in our patients, values of renal blood flow higher after than before CsA would then be expected.

Of interest, creatinine clearance measured simultaneously to GFR was unaltered by CsA, whereas GFR decreased, thus resulting in a marked (31-
overestimation of true GFR by creatinine clearance. This may be the consequence of excessive tubular secretion of creatinine resulting from CsA administration. Although alteration in renal function per se is associated with an overestimation of true GFR by creatinine clearance, the degree of renal impairment observed in the present study is much less than previously reported. In the absence of associated abnormalities in tubular function (no detectable changes in urinary excretion of β2-microglobulin or renal concentrating ability), it is suggested that CsA may directly alter the tubular handling of creatinine.

Experimental studies of the acute or short-term effects of CsA have suggested that an enhanced activity of the sympathetic nervous system27 and the renin-angiotensin system22 may contribute to the maintenance of intrarenal vasoconstriction. In addition, an excessive production of thromboxane A2, a vasoconstrictive metabolite of arachidonic acid, has been observed in CsA-treated animals as well as humans, and acute administration of a thromboxane synthetase inhibitor to CsA-treated renal transplant recipients has been reported to increase GFR.28 In our studies, the increase in renal vascular resistance induced by CsA therapy was associated with a consistent fall in the circulating renin level. A CsA-associated decrease in PRA was also observed in renal transplant recipients29 as well as patients with autoimmune diseases.6 This contrasts with the direct stimulation of renin release by isolated rat juxtaglomerular cells30 and the activation of the system usually occurring after acute or short-term administration of CsA in rats.22 The presently observed fall in renin release associated with CsA, in the absence of an increase in sodium intake (as assessed by 24-hour urinary sodium excretion) may be the consequence of the rise in systemic arterial pressure per se, expansion of the extracellular fluid volume,31 or a defect in the activation of prorenin.32

Alternatively, renal vasoconstriction could result from a defect in intrarenal release of vasoactivating substances such as kinins and prostaglandins. It was proposed that CsA-induced early renal vasoconstriction involves an alteration in eicosanoid metabolism before any modification in the renin-angiotensin system and the renal nerves is noted.33 The decrease in urinary prostaglandin excretion observed in some studies may be due to a direct effect of CsA on intrarenal synthesis27,34 or may occur via a decrease in the intrarenal production of kallikrein.35 In the present studies, a fall in urinary kallikrein, the renal enzyme that results in the intrarenal generation of kinins, was observed, which confirmed previous observations made in patients with rheumatoid arthritis.6,36 Such a marked decrease in urinary kallikrein occurred in the absence of a change in aldosterone and may have resulted from a structural or a functional alteration in distal tubular cells, which are the main site of kallikrein synthesis and release.35 A decreased urinary excretion rate of kallikrein has been observed in hypertensive patients with renal parenchymal disease37 and at least some subjects with essential hypertension and no obvious renal functional alteration.38 In fact, a diminished renal production of kallikrein could account for many of the renal abnormalities associated with CsA toxicity. A direct correlation between urinary excretion rate of kallikrein and renal blood flow has been observed in white essential hypertensive men.39 Second, kallikrein is a potential determinant of distal renal tubular sodium handling through the production of kinins or a direct effect of sodium channels.40 Finally, in vitro at least, kallikrein is a potent activator of prorenin.41

The lack of significant change in plasma aldosterone concentration was observed in the presence of a decrease in circulating renin but may be inappropriate with regard to the concomitant increase in serum potassium.29 These observations suggest that hyporeninemia or a relative tubular insensitivity to aldosterone may contribute to the observed increase in serum potassium.

In conclusion, cyclosporine given at moderate dosage to young diabetic adults with normal pretreatment arterial pressure and renal function is associated with a rise in arterial pressure, renal vasoconstriction, a decrease in GFR and proximal (as suggested by the exaggerated secretion of creatinine) as well as distal (as suggested by the fall in urinary kallikrein) tubular abnormalities. Most of these alterations are reversible within 3 months after cessation of cyclosporine therapy. In addition, in patients with a slight alteration in renal function induced by cyclosporine treatment, creatinine clearance is an unreliable index of GFR.

References


KEY WORDS • renin function • kallikrein • cyclosporine • renin • diabetes
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