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Renal vascular responses to captopril and to candesartan in patients with type 1 diabetes mellitus

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Background. Enhanced renal vasodilator responses to angiotensin-converting enzyme (ACE) inhibition in diabetes mellitus despite a normal or low plasma renin activity level have suggested intrarenal activation of the renin-angiotensin system in this disease. There is, however, a continuing debate as to the mediators of the renal hemodynamic response to ACE inhibition–reduced angiotensin II formation or pathways involving kinins, prostaglandins, and nitric oxide.

Methods. Twelve patients with type 1 diabetes mellitus of 18 ± 3.2 (SEM) years of duration (7 females and 5 males, ages 17 to 50, 32 ± 4.0 years) who were free of sustained microalbuminuria and on a high-salt diet were given the ACE inhibitor captopril (25 mg orally) on one day and the AT_1 receptor blocker candesartan (16 mg orally) on another day. Renal plasma flow (RPF) and glomerular filtration rate were measured before and for four hours after administration.

Results. Both drugs caused a significant increase in RPF (captopril 574 ± 26 to 625 ± 37 mL/min/1.73 m^2, $P = 0.008$; candesartan 577 ± 26 to 643 ± 37, $P = 0.004$). There was a highly significant correlation between the responses to captopril and to candesartan ($r = 0.86$, $P < 0.001$). Seven subjects had an RPF response to captopril that was accentuated (90 ± 13 mL/min/1.73 m^2), while five had a response that was normal (−4 ± 9). There was no significant change in glomerular filtration rate on either drug.

Conclusion. The remarkable rise in RPF in response to captopril and candesartan despite high-salt balance suggests the intrarenal activation of the renin-angiotensin system in diabetes that is not reflected in plasma renin levels. The high correlation between the renal hemodynamic response to captopril and to candesartan indicates that reduced angiotensin II formation is the main mechanism of action of the ACE inhibitor.

Key words: ACE inhibition, renin-angiotensin system, AT_1 receptor blocker, renal plasma flow, hemodynamics, vascular tone.

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The unambiguous effectiveness of angiotensin-converting enzyme (ACE) inhibition with captopril in changing the natural history of nephropathy in patients with type 1 diabetes mellitus has focused attention on the mechanisms by which the ACE inhibitor works [1]. Studies in humans and in animals have suggested that renal hemodynamics contribute to the pathogenesis [2–11]. For these reasons, a number of studies have been performed on the acute renal hemodynamic response to ACE inhibition in patients with type 1 diabetes mellitus [12–21]. The mechanism responsible for the acute and often dramatic vasodilator response to captopril has not been clearly defined. One possibility involves a reduction in angiotensin II (Ang II) formation, but there is an alternative possibility involving activation of vasodilator pathways via bradykinin accumulation, prostaglandin formation, and activation of nitric oxide synthesis [22].

In this study, we have assessed the mechanism responsible for the accentuated renal hemodynamic response to captopril in patients with type 1 diabetes mellitus by comparing that response to the response induced by an Ang II subtype 1 (AT_1) receptor blocker, candesartan. Our hypothesis was that the responses would correlate well if the dominant action of captopril involved blockade of Ang II formation, but would likely be discordant if the alternative action of captopril via vasodilator pathways was responsible.

METHODS

Subjects and protocols

We studied 12 men and women with type 1 diabetes mellitus who ranged in age from 17 to 50 years (mean ± SEM, 32 ± 4.0). The duration of diabetes ranged from 2 to 40 years (mean 18 ± 3.2). Type 1 diabetes mellitus was diagnosed according to accepted guidelines [23]. All were otherwise healthy, normotensive, and free of sustained microalbuminuria and other complications of diabetes. The subjects were studied during admission to a

metabolic ward at the General Clinical Research Center (GCRC) at the Brigham and Women's Hospital, where balance was achieved on a controlled diet.

All subjects were placed on a high-salt isocaloric diet starting two days prior to admission and continuing throughout the hospitalization, with a daily sodium intake of 200 mmol. Daily dietary potassium (100 mmol) and fluid intake (2500 mL) were constant. Twenty-four–hour urine samples were collected daily and analyzed for sodium, potassium, creatinine, and protein. The protocol was approved by the Human Subjects Committee of the institution, and written-informed consent was obtained from each subject.

Renal hemodynamic and hormonal responses to captopril and candesartan

Each subject participated in two experimental days. On the morning of each study day, an intravenous catheter was placed in each arm of each subject, one for infusion of p-aminohippurate (PAH), inulin, and dextrose 5% in water and the other for blood sampling. A third intravenous line was placed for continuous infusion of insulin that was started at 0.015 U/kg/h. Blood glucose was measured every 30 minutes (Precision PCX; Abbott Laboratories, Chicago, IL, USA). The insulin infusion was adjusted to maintain blood glucose below the renal threshold but without inducing hypoglycemia, at levels of 100 to 140 mg/dL. The subjects were supine and had been fasting for at least eight hours. Each study day began with a 60-minute baseline infusion of PAH and inulin prior to drug administration to determine baseline renal plasma flow (RPF) and glomerular filtration rate (GFR), respectively. Hormonal measurements were made on blood samples obtained at baseline and at four and eight hours after drug administration while the subjects were lying supine.

The study was designed to compare the renal hemodynamic response to captopril and to candesartan. On the first morning, the patients received captopril (25 mg orally). On the next morning, the patients received candesartan (16 mg orally). These doses were chosen because both represent the top of the relationship between dose and RPF response.

Blood pressure was recorded during each infusion by an automatic recording device (Dinamap; Critikon, Tampa, FL, USA) at five-minute intervals.

Renal clearance studies

Para-aminohippurate (PAH; Merck, Sharp & Dohme, Rahway, NJ, USA) and inulin (Inutest; Fresenius Pharma Austria GmbH, Linz, Austria) clearances were assessed after metabolic balance was achieved. A control blood sample was drawn, and then loading doses of PAH (8 mg/kg) and inulin (50 mg/kg) were given intravenously. A constant infusion of PAH and inulin was initiated immediately at a rate of 12 and 30 mg/min, respectively, with an IMED pump (Alaris Medical System, San Diego, CA, USA). This achieved a plasma PAH concentration in the middle of the range in which tubular secretion dominates excretion. At this plasma level of PAH, clearance is independent of plasma concentration and represents approximately 90% of RPF when corrected for individual body surface area. Likewise, at the level of plasma inulin achieved, inulin clearance reflects GFR. RPF and GFR determinations were made at baseline and at 45-minute intervals thereafter until 225 minutes (~4 h) while the subjects were supine.

Laboratory procedures

Blood samples were collected on ice and spun immediately, and the plasma was frozen until assay. Urinary and serum sodium and potassium levels were measured using the ion-selective electrode. PAH and inulin were measured using an autoanalyzer technique. Plasma renin activity (PRA) and aldosterone were determined by radioimmunoassay [24, 25]. Hemoglobin A1C (HbA1C) was measured by high-performance liquid chromatography. The normal range is 4.4 to 6.3%.

Analyses

Group means were calculated with the SEM as the index of dispersion. For renal hemodynamic data, the baseline value taken was the average of three predrug determinations, and the peak response was the average of the two highest consecutive values.

Pearson's correlation was used to test the association of the renal response to candesartan with the response to captopril. Paired *t*-test was used to compare the renal vascular and PRA responses to captopril and candesartan. The subjects were then divided into two groups: those in whom the RPF response to captopril was normal and those in whom the response was accentuated to determine whether there were differences in renin activity. Fisher's exact test, *t*-test, and Mann–Whitney rank sum test were used to compare the characteristics and the renal hemodynamic and PRA responses of these two groups. Analysis of covariance (ANCOVA) was performed to account for possible confounding effects of baseline characteristics on RPF response to the two drugs.

RESULTS

Baseline characteristics of the subjects are listed in Table 1. The high-salt balance, as evidenced by a 24-hour urine sodium excretion of 254 ± 34.9 mEq, resulted in suppression of the renin-angiotensin system (RAS) at baseline, as anticipated.

The average blood glucose achieved during the captopril study was not significantly different from that during the candesartan study (119 ± 35 vs. 127 ±38 mg/dL, $P =$

Table 1. Baseline characteristics of the 12 subjects in high-sodium balance

Parameters	Mean ± SEM
Age *years*	32 ± 4.0
Sex distribution *male/female*	5/7
Race	All Caucasian
Body mass index *kg/m²*	25 ± 1.0
Systolic blood pressure *mm Hg*	114 ± 4.4
Diastolic blood pressure *mm Hg*	67 ± 3.8
Duration of diabetes *years*	18 ± 3.2
Hemoglobin A1C %	7 ± 0.4
Fasting blood sugar *mg/dL*	124 ± 9.7
Serum creatinine *mg/dL*	0.82 ± 0.04
Serum sodium *mEq/L*	138 ± 0.7
Serum potassium *mEq/L*	4.4 ± 0.1
24-Hour urine sodium *mEq*	254 ± 34.9
24-Hour urine potassium *mEq*	59 ± 5.9
Plasma renin activity *ng Ang I/mL/h*	0.43 ± 0.08
Plasma aldosterone *ng/mL*	3.3 ± 0.6

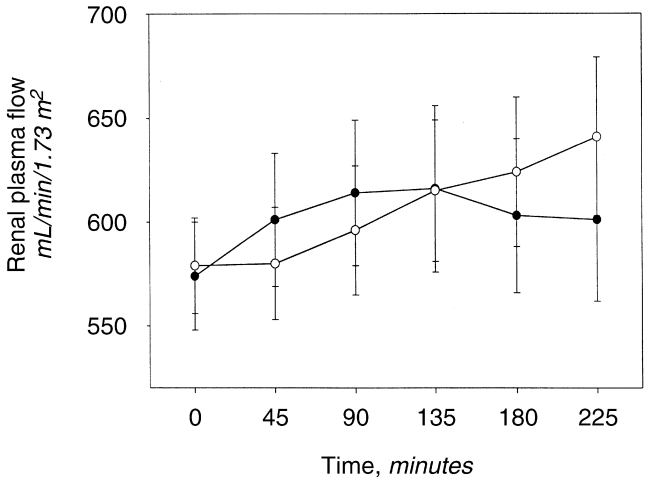

Fig. 1. Time course of the renal vascular response to captopril (●) and candesartan (○) in patients with type 1 diabetes mellitus.

Table 2. Baseline renal hemodynamics and the responses to captopril and candesartan (mean ± SEM)

	Captopril	Candesartan	Captopril vs. candesartan *P* value
Renal plasma flow *mL/min/1.73 m²*			
Baseline	574 ± 26	577 ± 26	0.69
Peak	625 ± 37	643 ± 37	0.09
Response	51 ± 15	66 ± 19	0.13
Glomerular filtration rate *mL/min/1.73 m²*			
Baseline	129 ± 4	125 ± 3	0.06
Peak	130 ± 4	127 ± 3	0.22
Response	1 ± 2	2 ± 2	0.63

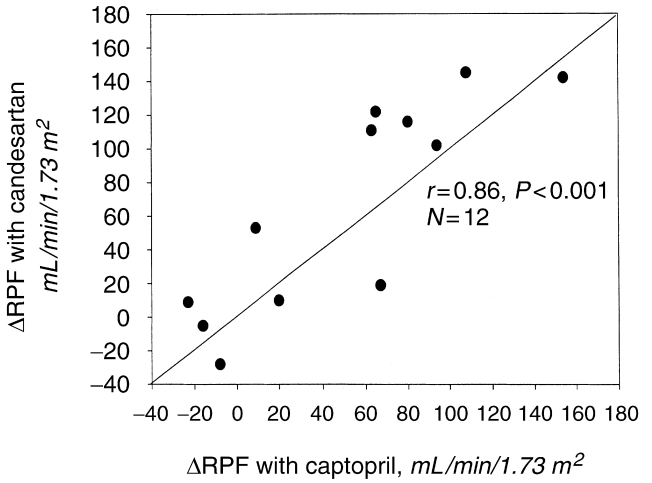

Fig. 2. Correlation between change in renal plasma flow (RPF) in response to captopril and to candesartan. Note the striking correlation ($r = 0.86$) between the responses to the two agents. In five of the seven patients with an accentuated response, the response to candesartan exceeded the response to captopril. Thus, it is unlikely that factors beyond Ang II are responsible for the accentuated response ($N = 12$; $P < 0.001$).

0.38). RPF at baseline was not significantly different for the two drugs (Table 2). Both captopril and candesartan caused a rise in RPF with time (Fig. 1). Captopril caused a significant increase in RPF of 51 ± 15 mL/min/1.73 m² (peak vs. baseline RPF, $P = 0.008$). Candesartan likewise induced a substantial rise in RPF of 66 ± 19 mL/min/1.73 m² ($P = 0.004$). The response to captopril was not significantly different from the response to candesartan ($P = 0.13$); however, the time to peak was different for the two drugs. Captopril had achieved the greatest response by 90 to 135 minutes, while the response to candesartan was still rising at 225 minutes. Baseline and peak GFRs were likewise not significantly different between the two drugs. There was no significant change in GFR either in response to captopril or to candesartan ($P = 0.74$ and $P = 0.45$, respectively).

The RPF responses to captopril and to candesartan showed remarkable concordance ($r = 0.86$, $P < 0.001$; Fig. 2). With an r^2 of 0.74, 74% of the variation in the response to captopril was accounted for on the basis of the response to candesartan. Using ANCOVA, there was no significant difference between the RPF response to the two drugs ($P = 0.239$). When baseline RPF, baseline GFR, and baseline PRA were added as covariates, the responses remained not significantly different from each other ($P = 0.345$).

Plasma renin activity levels were equally suppressed at baseline on both days (Table 3). The PRA response to captopril did not differ from the response to candesartan (Table 3), although a trend toward a larger response to candesartan was evident.

The RPF response to captopril in normal humans when the renin system is suppressed by a high-salt diet is less than 30 mL/min/1.73 m² [26, 27]. On that basis,

Table 3. Baseline plasma renin activity (PRA) values (ng Ang I/mL/h) and the responses to captopril and candesartan (mean ± SEM)

	Captopril	Candesartan	Captopril vs. candesartan *P* value
Baseline	0.43 ± 0.08	0.52 ± 0.12	0.18
Peak	1.05 ± 0.55	5.75 ± 3.20	0.14
Response	0.62 ± 0.47	5.23 ± 3.11	0.14

the response to captopril in the 12 patients with type 1 diabetes mellitus was normal in five and accentuated in the other seven. In the five patients in whom the response to captopril was minimal, the response to candesartan was also minimal. In the seven patients in whom the response to captopril was accentuated, the response to candesartan was accentuated equally or more (Fig. 2). The seven patients with the accentuated response did not differ from the five with normal RPF responses in terms of gender ($P = 1.000$), age (30 ± 4.7 vs. 36 ± 8.9 years, $P = 0.52$), fasting blood sugar (123 ± 17 vs. 123 ± 7 mg/dL, $P = 0.99$), or HbA1C (7.3 ± 0.5 vs. 6.4 ± 0.5%, $P = 0.22$) nor in terms of the average blood glucose level achieved following captopril (120 ± 8 vs. 117 ± 8 mg/dL, $P = 0.82$) or candesartan (128 ± 10 vs. 127 ± 10 mg/dL, $P = 0.94$). Moreover, the two groups did not differ either in baseline PRA or in PRA response (Table 4). However, there was a significant difference in baseline RPF between the groups. On both study days, the patients who showed an accentuated RPF response had higher baseline RPF than those who showed a normal response (captopril 623 ± 26 vs. 505 ± 44 mL/min/1.73 m^2, $P = 0.04$; candesartan 625 ± 28 vs. 509 ± 32, $P = 0.02$; Fig. 3).

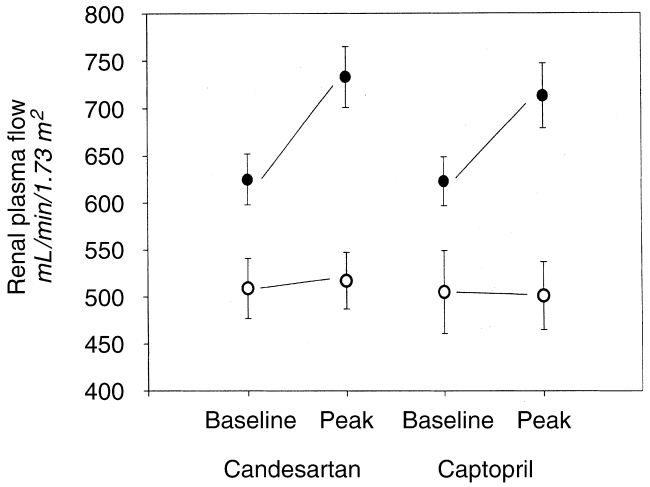

Fig. 3. Baseline and peak renal plasma flow (RPF) response to candesartan and to captopril in the patients with type 1 diabetes mellitus subdivided according to whether the renal response to captopril was in the normal range or accentuated. Note that baseline RPF was significantly higher in the patients in whom the renal hemodynamic response to captopril, and to candesartan, was accentuated. Symbols are: (●) accentuated response; (○) normal response.

DISCUSSION

Our goal was to ascertain whether or not the mechanism for the enhanced renal hemodynamic response to ACE inhibition in patients with type 1 diabetes mellitus was predominantly caused by reduced Ang II formation [12–21]. Few studies have attempted to delineate this mechanism in humans, and these have largely focused on normal subjects on a low-salt diet in order to activate the RAS [28–30]. This study in diabetic patients on a high-salt diet has therapeutic implications, given that this population has been shown to benefit from ACE inhibition and that their typical diet more likely includes liberal salt intake rather than rigid sodium restriction.

Both captopril and candesartan induced significant increases in RPF. Because RPF determinations were not made beyond 225 minutes, it might seem that the peak response to candesartan was not captured. However, we have previously shown that the RPF response already reaches its peak in the first four hours and is sustained for the next four hours [31]. The correlation coefficient between the RPF responses to captopril and to candesartan was 0.86 ($P < 0.001$). As candesartan specifically blocks the AT_1 receptor to prevent the action of Ang II, this implies that the dominant effect of ACE inhibition was likewise on the Ang II pathway. Thus, it is unlikely that other pathways, such as those involving bradykinin, prostaglandin, and nitric oxide, contribute substantially to the renal response to ACE inhibition in accord with other observations in humans [32]. The same conclusion was reached in a study by Gansevoort, De Zeeuw, and De Jong in normal subjects, in whom the Ang II antagonist losartan had effects on renal hemodynamics similar to the ACE inhibitor enalapril [33]. However, unlike their study, ours includes a patient-by-patient analysis rather than a comparison of group means.

Although indirect, this approach to testing our hypothesis is one of the few methods available in humans. In two earlier studies, the same principle of a shared action of two pharmacologically distinct drugs—an ACE inhibitor and an Ang II antagonist—was also involved in explaining the renal hemodynamic effects of ACE inhibition [28, 29]. The only other mechanistic study in humans involved administration of captopril alone, captopril plus the bradykinin receptor antagonist, icatibant (HOE 140), or losartan alone. Renal vascular resistance decreased to a similar extent in all three phases, indicating that bradykinin did not play a significant role in the renal response to ACE inhibition [30].

One possible limitation of this study involves the fact

Table 4. Renal plasma flow (mL/min/1.73 m^2) and plasma renin activity (ng Ang I/mL/h) on captopril and candesartan and on high-salt diet among the normal-RPF and accentuated-RPF response groups (mean ± SEM)

	Normal subjects	Type 1 DM normal RPF response group	Type 1 DM accentuated RPF response group	Type 1 DM accentuated vs. normal RPF response group
Captopril				
RPF response	7 ± 21	−4 ± 9	90 ± 13	<0.001
Baseline PRA	0.3 ± 0.1	0.34 ± 0.08	0.49 ± 0.14	0.43
Peak PRA	3.4 ± 1.1	0.62 ± 0.17	1.49 ± 1.17	0.46
PRA response	3.1	0.28 ± 0.09	1.00 ± 1.01	0.42
Candesartan				
RPF response	93 ± 23[a]	8 ± 15	108 ± 17	<0.001
Baseline PRA	0.45 ± 0.05[a]	0.38 ± 0.13	0.61 ± 0.19	0.53
Peak PRA	10.62 ± 3.96[a]	1.10 ± 0.55	9.62 ± 6.41	0.17
PRA response	10.17 ± 3.60[a]	0.72 ± 0.43	9.01 ± 6.24	0.24

[a] Unpublished results from our laboratory

that the sequence of captopril and candesartan administration was not random. Our goal was to study the response to the two agents in as short an interval as possible, and candesartan has a duration of action of at least 48 hours [31]. Captopril, on the other hand, shows a response that fades rapidly after two to three hours [34]. For that reason, captopril was administered first in each subject. Our thesis was that if the response to captopril had a duration longer than we anticipated, it would have been expressed in baseline PRA level and RPF prior to candesartan administration. As both measures were essentially identical at baseline on the two days, it is unlikely that a sustained action of captopril influenced the results. However, despite this observation, the possibility of a carryover effect cannot be ruled out with certainty.

There is evidence of RAS activation in diabetic subjects who are hyperglycemic. In Miller et al's study on type 1 diabetic patients, hyperglycemia produced higher PRA levels compared with euglycemia, both at baseline when patients were lying supine and during periods of orthostatic stress induced by lower body negative pressure [35]. To assess further the implications for the kidney of the RAS activation in patients with type 1 diabetes, the same investigator reported decreased baseline effective RPF (ERPF) and renal blood flow (RBF) after inducing hyperglycemia over a period of approximately 12 hours and a significant increase in ERPF upon administration of the Ang II antagonist losartan while maintaining a hyperglycemic state. There was no significant change in either ERPF or RBF during euglycemia [36]. These experiments support the hypothesis that hyperglycemia affects renal hemodynamics by activating the RAS.

Activation of the RAS in these subjects with type 1 diabetes suggested strongly by the highly concordant renal hemodynamic response to captopril and to candesartan was not evident in measures of PRA. By this index the renin system was suppressed, as anticipated, from the high-salt intake. These observations suggest the possibility of intrarenal activation of the RAS that is not reflected in plasma levels. A similar pattern occurs in normal humans when hyperglycemia enhances the renal hemodynamic response to pharmacological interruption of the renin system, yet PRA remains unchanged [26, 27].

Another feature of the renal hemodynamic response to hyperglycemia was also evident in our patients. Hyperglycemia induced acutely over a period of one hour increases RPF and also increases the response to pharmacological interruption with ACE inhibitors and Ang II antagonists [26, 27]. This paradoxical relationship, a larger renal vasodilator response to pharmacological interruption of the renin system being associated with higher RPF at baseline, was evident not only in our patients with type 1 diabetes in this study, but also in patients with type 2 diabetes and nephropathy as we have reported recently [37]. Thus, it is possible that the forces responsible for vasodilation and the forces responsible for activation of the intrarenal RAS are in some way related. Studies by our group are currently being undertaken to investigate the factors determining the level of baseline RBF (abstract; Laffel et al, *J Am Soc Nephrol* 9:117a, 1998). The possibility of genetic determinants, for example ACE gene polymorphisms, is especially attractive, although the present study was not powered to address this issue. In animal studies, the renal hemodynamic response to hyperglycemia has been attributed, at least in part, to activation of nitric oxide synthase [38]. Moreover, there has been substantial recent interest in a continuing interaction between nitric oxide and RAS as part of normal renal homeostasis [39].

How does hyperglycemia activate the RAS? One might invoke a reduced extracellular fluid volume from osmotic diuresis as the mechanism. Other studies, however, show no evidence of intravascular volume depletion during hyperglycemia [32, 40]. In a study by Woods, Mizelle, and Hall, a tubuloglomerular feedback mechanism was implicated since intrarenal infusion of glucose

in rats resulted in an increased renin secretion rate to greater than twice the control level, but only in filtering kidneys [41].

The remarkable concordance in the renal hemodynamic response to the ACE inhibitor captopril and the AT_1 receptor blocker candesartan makes it exceedingly likely that the exaggerated response reflects reversal of an increase in angiotensin-mediated renal vascular tone. That, in turn, probably reflects an increase in Ang II generation as the mediator. The absence of an increase in PRA in the patients who show the enhanced response points to intrarenal Ang II generation as the probable locus, in accord with observations that we have made in patients with type 2 diabetes mellitus and in normal subjects during infusion of glucose to maintain a stable level of hyperglycemia below the threshold for glycosuria [26, 27, 42]. Activation of the intrarenal RAS in patients with diabetes provides a powerful rationale for the effectiveness of therapeutic agents that block this system. The specific factors responsible for activation of the RAS beyond hyperglycemia and the implications of this activation on the pathogenesis of nephropathy both require substantial additional investigation.

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