Change in the Distribution of Albuminuria According to Estimated Glomerular Filtration Rate in Pima Indians With Type 2 Diabetes

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OBJECTIVE — We examined secular trends in the frequency distribution of albuminuria and estimated glomerular filtration rate (eGFR) in subjects with type 2 diabetes in 1982–1988 and 2001–2006, two periods associated with major changes in the management of diabetes.

RESEARCH DESIGN AND METHODS — The cross-sectional study included Pima Indians ≥15 years old with type 2 diabetes and measures of serum creatinine and urinary albumin-to-creatinine ratios (ACR). The continuous probability density distributions of ACR and eGFR were compared for the two time periods. eGFR was calculated using the Modification of Diet in Renal Disease Study equation.

RESULTS — The overall standardized distribution of ACR shifted toward lower values between time periods ($P = 0.001$), whereas the standardized distribution of eGFR did not ($P = 0.45$). In the first period, eGFR was <60 ml/min per 1.73 m^2 in 6.5% of the 837 subjects. Of these, 9.3% had normal ACR, 7.4% had microalbuminuria, and 83.3% had macroalbuminuria. In the second period, the prevalence of low eGFR was similar (6.6% of the 1,310 subjects). Among those with low eGFR, normal ACR prevalence doubled to 17.2%, microalbuminuria prevalence nearly tripled to 19.5%, and macroalbuminuria prevalence declined to 63.2%. Twice as many subjects in the second period received antihypertensive medicines and 30% more received hypoglycemic medicines than in the first period.

CONCLUSIONS — The distribution of albuminuria changed significantly among diabetic Pima Indians over the past 20 years, as treatment with medicines to control hyperglycemia and hypertension increased. The distribution of eGFR, however, remained unchanged. Consequently, the frequency of chronic kidney disease characterized by normoalbuminuria and low eGFR doubled.

Diabetes Care 32:1845–1850, 2009

Chronic kidney disease (CKD), characterized by a low glomerular filtration rate (GFR) in the absence of elevated urinary albumin excretion, has been increasingly identified as a frequent finding among individuals with diabetes (1–5). Whether this finding represents nondiabetic kidney disease, a variant of diabetic kidney disease, or changes in treatment is uncertain. In type 1 diabetes, normoalbuminuric women with low GFR were found to have more advanced glomerular lesions than normoalbuminuric women with normal GFR (4). On the other hand, another study that included both type 1 and type 2 diabetic subjects with low GFR reported that the risk of CKD progression or death was lower in those with normoalbuminuria than in those with elevated urinary albumin excretion (5).

In the present study, we examined the frequency distribution of albuminuria and estimated GFR (eGFR) in Pima Indians with type 2 diabetes in two time periods characterized by different therapeutic management of diabetic kidney disease to determine whether a change in the distribution occurred and if this change might be related to changes in management.

RESEARCH DESIGN AND METHODS

— Since 1965, each individual ≥5 years old who resides in the Gila River Indian Community in Arizona has been invited to participate in a research examination approximately every 2 years, regardless of health. These biennial examinations include measurements of venous plasma glucose concentration obtained 2 h after a 75-g oral glucose load and assessment for the complications of diabetes. Diabetes was diagnosed by 1985 World Health Organization criteria (6), and the date of diagnosis was determined from these research examinations or from review of clinical records if diabetes was diagnosed in the course of routine medical care. Since 1 July 1982, albumin concentration was measured with a nephelometric immunoassay in urine specimens collected at the end of the 2-h glucose tolerance test (7). Values <6.8 mg/l, the threshold beneath which albuminuria cannot be detected by the assay, were assigned the value of 6.8 mg/l. Urine creatinine concentration in the same specimen and serum creatinine were measured by a modification of the Jaffé reaction (8). Elevated albuminuria was defined by a urinary albumin-to-creatinine ratio (ACR) ≥30 mg/g. eGFR was determined using the four-variable Modification of Diet in Renal Disease (MDRD) Study equation (9) (using the racial classification of non-

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Received 29 December 2008 and accepted 18 June 2009.
Published ahead of print at http://care.diabetesjournals.org on 10 July 2009. DOI: 10.2337/dc08-2325.
The findings and conclusions in this presentation have not been formally disseminated by the Centers for Disease Control and Prevention and should not be construed to represent any agency determination or policy.

black for American Indians), and an eGFR of <60 ml/min per 1.73 m^2 was considered low. BMI was defined as weight in kilograms divided by the square of height in meters. Mean arterial pressure (MAP) was calculated as MAP = ⅔ diastolic arterial pressure + ⅓ systolic arterial pressure. HbA_1 was measured by agar gel electrophoresis (10) through December 1989, and A1C was measured by high-performance liquid chromatography (11) thereafter. The correlation between the two measures was 0.92, as shown in a previous study, and a linear regression formula A1C = 0.99 × HbA_1 − 1.535 was used to estimate A1C in the 794 subjects in whom HbA_1 was measured (12). The study population included subjects who resided in the community at any time from 1 July 1982 through 30 June 1988 and from 1 January 2001 through 31 December 2006, attended research examinations at ≥15 years of age, and had diabetes.

Statistical analysis

Population characteristics are presented as means ± SD or medians (25th and 75th percentiles). Normally distributed variables were compared with general linear models adjusted for age and sex. Variables with nonnormal distributions were log transformed before comparison. Binomial variables were similarly adjusted using multiple logistic regression.

The study is a cross-sectional comparison of two time periods. The prevalence of elevated albuminuria was computed for the two time periods, using data from the research examination closest to the midpoint of each period. Likewise, the prevalence of antihypertensive and hypoglycemic treatments was computed for the two time periods as the proportion of subjects who were receiving these medicines at the research examination closest to the midpoint of these periods. Treatment was assessed from self-report of subjects at each research examination. Complete data on specific classes of antihypertensive medicines were available beginning in April 1992, so the proportion treated with renin-angiotensin system (RAS) (ACE inhibitors and angiotensin receptor antagonists) inhibitors was computed for the late period only. Treatment with RAS inhibitors was introduced in the Gila River Indian Community in November 1986, with only limited use until September 1989, so the use of these drugs during the early period was extremely limited.

Table 1—*Clinical and demographic characteristics of Pima Indians with diabetes in two time periods*

	1982–1988	2001–2006	*P**
n	837	1,310	
Women	295	474	
Men	542	836	
Age (years)	46.4 ± 14.5	44.2 ± 13.4	0.0005†
Diabetes duration (years)‡	7.4 (2.0–14.8)	7.6 (2.0–15.0)	0.04
BMI (kg/m²)	32.9 ± 7.2	37.0 ± 8.9	<0.0001
Fasting plasma glucose (mmol/l)	11.3 ± 4.5	9.8 ± 4.3	<0.0001
A1C (%)	8.3 ± 2.6	8.4 ± 2.4	0.3
MAP (mmHg)	93.0 ± 13.1	91.3 ± 12.5	0.01
eGFR (ml/min per 1.73 m²)	115.3 ± 35.6	116.8 ± 38.1	0.2
Serum creatinine (μmol/l)	72.4 ± 45.0	71.2 ± 35.4	0.9
ACR (mg/g)‡	27.6 (12.8–159.7)	22.0 (10.3–95.1)	0.01
CKD (%)	47.9	43.6	0.2
Antihypertensive medicines (%)	19.8	51.1	<0.0001
RAS inhibitors (%)	—	41.3	
Hypoglycemic medicines (%)	42.0	54.4	<0.0001

Data are unadjusted means ± SD or median (25th–75th percentile). CKD is defined as eGFR <60 ml/min per 1.73 m² or ACR ≥30 mg/g. In the early time period, data were missing for BMI in 7 subjects, for fasting plasma glucose in 57 subjects, for A1C in 40 subjects, and for MAP in 5 subjects. In the late period, data were missing for BMI in 28 subjects, for fasting plasma glucose in 22 subjects, for A1C in 1 subject, and for MAP in 9 subjects. **P* values were adjusted for age and sex, unless otherwise indicated. †Adjusted for sex. ‡Median.

The continuous probability density distributions of ACR and eGFR were estimated for each time period; ACR distributions were also estimated for subjects with normal or low eGFR in each time period. To account for changes in the underlying distribution of confounding variables between the two time periods, ACR and eGFR from the late time period were standardized to those of the early period by indirect adjustment for the three-way categorizations of age, sex, and diabetes duration. A total of 20 strata were used (age × sex × diabetes duration: 2 × 2 × 5) in the adjustment. The standardized eGFR and logarithmic ACR distributions in the two time periods were then compared using the Kolmogorov-Smirnov test. Smoothed distributions were estimated using SAS proc kde. Density values of ACR correspond to the density of the distribution of the logarithm of ACR. For clarity, values of untransformed ACR are shown on a logarithmic scale, which has an identical relative distribution.

RESULTS — Clinical and demographic characteristics of the diabetic subjects in the two time periods are presented in Table 1. More subjects received hypoglycemic and antihypertensive medicines in the late time period (54.4 and 51.1%, respectively) than in the early period (42.0 and 19.8%, respectively). Although subjects in the late period had longer mean duration of diabetes and higher mean BMI than those included in the early period, their fasting plasma glucose, MAP, and ACR were significantly lower. A total of 223 subjects were included in both time periods.

In the early period, 6.5% (n = 54) of the 837 subjects with type 2 diabetes had eGFR <60 ml/min per 1.73 m^2. Of these, 9.3% (n = 5) had normal ACR, 7.4% (n = 4) had microalbuminuria, and 83.3% (n = 45) had macroalbuminuria. Among the 1,310 diabetic subjects in the late period, the prevalence of low eGFR was similar: 6.6% (n = 87). Among those with low eGFR, the prevalence of normal ACR had nearly doubled to 17.2% (n = 15), the prevalence of microalbuminuria had nearly tripled to 19.5% (n = 17), and the prevalence of macroalbuminuria had declined to 63.2% (n = 55). The age- and sex-adjusted logarithm of the average ACR level changed significantly over time in the study population (P = 0.01) (Table 1), more significantly in those with low eGFR (P = 0.0003) than in those with normal eGFR (P = 0.02).

Clinical and demographic characteristics of those with eGFR <60 ml/min per 1.73 m^2 and elevated or normal ACR in the two time periods are presented in Table 2. Subjects with elevated ACR in the late period had higher BMI but lower

Table 2—*Clinical and demographic characteristics of diabetic Pima Indians with eGFR <60 ml/min per 1.73 m² and normal or elevated ACR in two time periods*

	Elevated ACR			Normal ACR		
	1982–1988	2001–2006	*P**	1982–1988	2001–2006	*P**
n	49	72		5	15	
Men	10	18		1	1	
Women	39	54		4	14	
Age (years)	60.0 (36.0–79.9)	56.7 (31.4–82.4)	0.1†	69.2 (50.0–84.9)	59.2 (44.2–75.8)	0.1†
Diabetes duration (years)‡	19.5 (0–37.4)	23.3 (3.2–39.6)	0.2	8.9 (0–19.6)	18.7 (6.6–35.7)	0.04
BMI (kg/m²)	29.0 (18.9–44.1)	33.9 (20.7–70.3)	0.003	28.8 (24.2–32.5)	40.1 (22.8–64.6)	0.1
Fasting plasma glucose (mmol/l)	9.3 (3.8–26.1)	8.7 (2.8–24.9)	0.4	9.4 (6.2–17.0)	7.9 (4.4–17.8)	0.3
A1C (%)	8.0 (4.0–13.5)	8.0 (5.1–13.1)	0.9	7.6 (5.5–12.1)	8.2 (5.5–13.1)	0.9
MAP (mmHg)	102.6 (69.3–150.0)	97.5 (62.0–135.3)	0.02	91.1 (80.0–97.3)	80.7 (56.0–94.0)	0.1
eGFR (ml/min/1.73 m²)	36.6 (5.4–58.9)	38.3 (10.9–60.0)	0.4	47.9 (35.2–56.7)	43.7 (21.7–57.5)	0.4
Serum creatinine (μmol/l)	191.4 (97.2–760.2)	173.9 (94.6–530.4)	0.1	122.0 (97.2–168.0)	133.2 (96.4–221.0)	0.4
ACR (mg/g)‡	3,943.6 (49.6–46,971.4)	1,944.7 (32.5–20,728.6)	0.001	20.0 (13.1–29.6)	12.1 (5.4–29.4)	0.2
Antihypertensive medicines (%)	64.6	93.1	0.0003	40.0	93.3	0.06
RAS inhibitors (%)	—	76.4		—	66.7	
Hypoglycemic medicines (%)	85.1	81.9	0.7	40.0	86.7	0.07

Data are unadjusted means or median (25th–75th percentile). In subjects with elevated ACR, data were missing for BMI in three subjects in the early time period and in six subjects in the late period; for fasting plasma glucose in three subjects in the early period and five subjects in the late period; for A1C in three subjects in the early period, and for MAP in one subject in the late time period. In subjects with normal ACR, data were missing for fasting plasma glucose in one subject in the late time period. **P* values adjusted for age and sex, unless otherwise indicated. †Adjusted for sex. ‡Median.

MAP and ACR than subjects in the early period. All but two of the subjects with low eGFR and normal ACR were women. Those with normal ACR in the late period had longer duration of diabetes than subjects in the early period. Moreover, >90% of the subjects in the late period received antihypertensive medicines ($n = 67$ with elevated ACR and $n = 14$ with normal ACR), and two-thirds of them were taking RAS inhibitors. They were also twice as likely to take hypoglycemic medicines as in the earlier time period, although the total number of subjects was quite small.

Table 3 shows unstandardized and standardized prevalence of eGFR and albuminuria categories in diabetic Pima Indians in the two time periods. Significant changes in the overall age-, sex-, and diabetes duration–standardized distribution of ACR occurred between time periods ($P = 0.001$) (Fig. 1). These changes were present in subjects with both normal eGFR ($P = 0.002$) and low eGFR ($P = 0.001$) (Fig. 2). In the low eGFR group, the distributional change reflects the increase in the frequency of normal ACR. No significant changes in the standardized distribution of eGFR ($P = 0.45$) (Fig. 1) or the adjusted prevalence of low eGFR occurred between time periods ($P = 0.42$).

Table 3—*Prevalence of eGFR and albuminuria categories in diabetic Pima Indians in two time periods*

	1982–1988	2001–2006	2001–2006 Standardized
Normal eGFR and normal ACR	436 (52.1)	739 (56.4)	57.7
Normal eGFR and elevated ACR	347 (41.5)	484 (36.9)	36.6
Low eGFR and normal ACR	5 (0.6)	15 (1.1)	1.1
Low eGFR and elevated ACR	49 (5.9)	72 (5.5)	4.6

Data are *n* (%) or %. Results for 2001–2006 are presented both unstandardized and standardized to the early period after adjustment for age, sex, and duration of diabetes. Normal eGFR, eGFR ≥60 ml/min per 1.73 m², low eGFR, eGFR <60 ml/min per 1.73 m²; normal ACR, ACR <30 mg/g; elevated ACR, ACR ≥30 mg/g.

CONCLUSIONS — The frequency distribution of albuminuria among diabetic Pima Indians has changed significantly over the past 20 years. The redistribution of ACR toward lower values without a concomitant change in eGFR has led to an increase in the proportion of those with CKD characterized by low eGFR and normoalbuminuria, a condition virtually nonexistent in diabetic Pima Indians in the 1980s. We are unaware of other studies that systematically examined time trends in the distribution of ACR and eGFR in a population with type 2 diabetes. The doubling in the prevalence of this condition over the past two decades coincides with the introduction and widespread use of more effective medicines to manage hyperglycemia and blood pressure in this community (13) and elsewhere. Although a causal relationship cannot be determined from an observational study, these results suggest that the finding of low eGFR and normal urinary albumin excretion in patients with type 2 diabetes is due, at least in part, to recent improvements in therapeutic management of diabetes and diabetic kidney disease rather than the emergence or recognition of an atypical form of diabetic kidney disease, as some have suggested (1,14,15). Despite the increase in the prevalence of normoalbuminuria in diabetic Pima Indians with low eGFR, the proportion of subjects with this condition remains low at about 1.2% of the diabetic population.

In the more recent time period, the

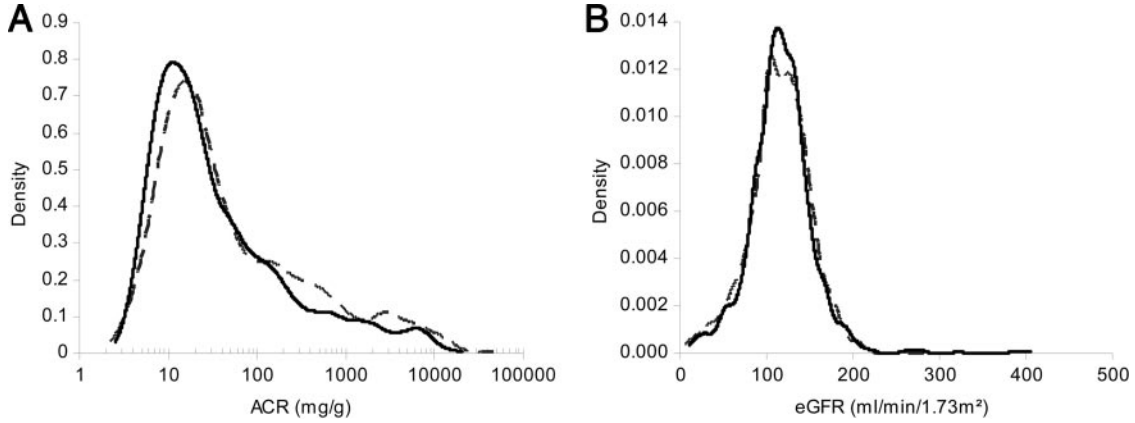

Figure 1—*Overall change in the continuous distribution of ACR (P = 0.001) (A) and the absence of change in the distribution of eGFR (P = 0.45) (B) between time periods. The distributions in the later period, illustrated by the solid line (n = 1,310), are age-, sex-, and diabetes duration–standardized to the early period, illustrated by the dashed line (n = 837).*

prevalence of normoalbuminuria among diabetic Pima Indians with low eGFR was 17.2%, consistent with studies in other diabetic populations from the same time period in which prevalence estimates ranged between 13 and 42% (1–5,14,16), but twice that of 9.3% found in the Pima Indians in the 1980s. Atherosclerosis may contribute to the appearance of low eGFR and normoalbuminuria in some diabetic populations (15), but in diabetic Pima Indians, clinical atherosclerosis generally occurs only after the onset of proteinuric CKD and hence is an unlikely explanation for normoalbuminuric CKD in this population (17). On the other hand, improved therapeutic management of diabetes may be a major contributing factor to the appearance of normoalbuminuria among diabetic patients with low eGFR in these diabetic populations. Indeed, studies in which diabetic patients taking RAS inhibitors were excluded from the analysis showed a significant reduction in the prevalence of normal albuminuria among those with low eGFR (3,5). To our knowledge, no one has examined the role of improved management of hyperglycemia on the appearance of normoalbuminuria among diabetic patients with low eGFR, yet there is abundant evidence that improvements in glycemic control reduce the frequency of elevated albuminuria in both types of diabetes (18–20). The extent to which RAS inhibitors and improved glycemic management contribute to the shift in ACR distribution, however, cannot be determined in this observational study.

We do not have morphological data from kidney biopsies in Pima Indians with CKD characterized by low eGFR and normal urinary albumin excretion. Nevertheless, postmortem histological examinations of the kidneys in diabetic and nondiabetic Pima Indians and morphological studies of kidney biopsies in Pima Indians with type 2 diabetes reveal that intercapillary glomerulosclerosis is by far the predominant form of kidney disease among diabetic Pima Indians (21). The extent to which the course of kidney disease in Pima Indians with low eGFR and normal urinary albumin excretion differs from that in Pima Indians with elevated urinary albumin excretion is not known. In the present study, only one person with CKD characterized by low eGFR and normoalbuminuria progressed to kidney failure, and this person developed elevated urinary albumin excretion as the disease progressed.

Because Pima Indians with diabetes often have substantially elevated GFR in the early years after diagnosis (22), a GFR <60 ml/min per 1.73 m^2 may represent a more significant loss of kidney function than in Caucasian populations with similar levels of CKD. With the use

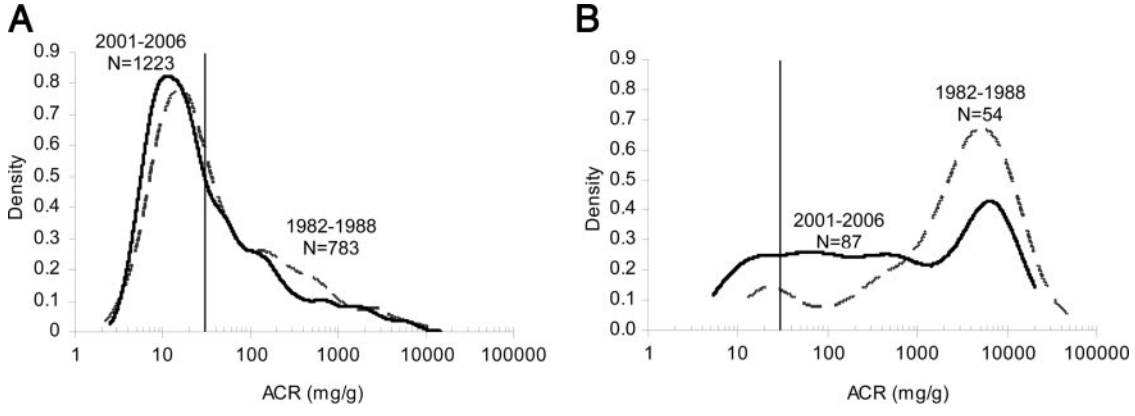

Figure 2—*Overall changes in the continuous distribution of ACR between time periods in subjects with normal eGFR ≥60 ml/min per 1.73 m^2 (P = 0.002) (A) and low eGFR <60 ml/min per 1.73 m^2 (P = 0.001) (B). In the low-eGFR group, the distributional change reflects the increase in the frequency of normal ACR. The distributions in the later period, illustrated by the solid line, are age-, sex-, and diabetes duration–standardized to the early period, illustrated by the dashed line. The vertical line in the graphs corresponds to ACR = 30 mg/g. N = number of subjects.*

of 90 ml/min per 1.73 m^2 to define low eGFR instead of 60 ml/min per 1.73 m^2, 20.5% of the diabetic subjects had low eGFR in the early period and 20.2% in the late period, with a higher proportion of subjects with low eGFR having normal ACR in the late period (39.0%) than in the early period (26.7%). By this definition of CKD, the overall change in the standardized distribution of ACR between time periods remained significant in subjects with normal or low eGFR (for the normal eGFR group: $P = 0.02$; for the low eGFR group: $P = 0.0001$). At higher GFR, however, the MDRD equation estimates are more biased (underestimating measured GFR for eGFR between 60 and 119 ml/min per 1.73 m^2 and overestimating measured GFR for eGFR ≥120 ml/min per 1.73 m^2) and less precise on both an absolute and percentage basis, particularly so among populations not included in the MDRD study, such as Pima Indians (23).

A total of 223 individuals were examined in both time periods. Because the lack of independence of these observations could affect the results, we repeated the analyses after randomly assigning each of these 223 individuals to only one of the time periods. By this approach, the differences between the ACR distributions in the two time periods were even greater and the conclusions of the study were unchanged (data not shown).

In summary, the distribution of albuminuria changed significantly among diabetic Pima Indians over the past 20 years without a concomitant change in the distribution of eGFR. As a result, the frequency of CKD characterized by normoalbuminuria and low eGFR in diabetic Pima Indians doubled and is now consistent with reports in other populations from the same time period. The frequency of low eGFR with normoalbuminuria increased significantly during a time when effective treatments for diabetes and diabetic kidney disease, which are known to lower albuminuria, were introduced, suggesting that improvements in therapeutic management are responsible, at least in part, for the emergence of this condition. Whether the clinical course in these patients differs from that in persons with more typical diabetic CKD characterized by elevated albuminuria is uncertain, but studies in Pima Indians suggest that newer treatments for diabetic kidney disease, while not preventing the development of kidney disease, may slow its progression and reduce the incidence of end-stage renal disease (24).

Acknowledgments— This research was supported by the Intramural Research Program of the National Institute of Diabetes and Digestive and Kidney Diseases. M.E.P. was supported by a Mentor-Based Fellowship award from the American Diabetes Association.

No potential conflicts of interest relevant to this article were reported.

Parts of this study were presented in poster-form at the th annual meeting of the American Diabetes Association, San Francisco, California, 6–10 June 2008.

We are indebted to the members of the Gila River Indian Community for participating in this investigation.

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