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Kidney disease among the Zuni Indians: The Zuni Kidney Project

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Kidney disease among the Zuni Indians: The Zuni Kidney Project.

Background. There is an epidemic of kidney disease among the Zuni Indians. In collaboration with health care providers and research institutions, the Zuni Pueblo established the Zuni Kidney Project to reduce the burden of kidney disease.

Methods. The Zuni Kidney Project conducted a population-based, cross-sectional survey to estimate the prevalence of albuminuria, hematuria, and related risk factors. Neighborhood household clusters served as the sampling frame. Participants completed a questionnaire, donated blood and urine samples, and had blood pressure, height, and weight measured. This survey provided the foundation for ongoing studies to identify genetic and environmental risk factors for disease susceptibility and progression.

Results. Age and gender distributions among survey participants were similar to those in the eligible Zuni population. Prevalence of incipient albuminuria (IA) (0.03≤ urine albumin:creatinine ratio, UACR <0.3) and overt albuminuria (OA) (UACR <0.3) were higher among diabetics [IA 34.3% (28.3, 40.4%); OA 18.6% (13.7, 23.6%)] than nondiabetics [IA 11.1% (9.3, 12.8%); OA 1.7% (1.0, 2.5%)]. Nondiabetics comprised 58.6% (52.2, 65.0%) and 30.9% (19.9, 41.9%) of participants with IA and OA, respectively. The prevalence of hematuria was higher among diabetics [≥ trace 47.0% (40.7, 53.4); ≥50 red blood cell/μL 25.8% (20.3, 31.4%)] than nondiabetics [≥ trace 31.1% (28.5, 33.7%); ≥50 red blood cell/μL 16.6% (14.5, 18.7%)]. Hypertension was associated with albuminuria among diabetic and nondiabetic participants. Hypercholesterolemia was associated with albuminuria among nondiabetic participants. Diabetes and alcohol use were associated with hematuria.

Conclusion. The high prevalences of albuminuria among nondiabetics and of hematuria among diabetics and nondiabetics are consistent with high rates of nondiabetic kidney disease among Zuni Indians with and without diabetes.

Resumen

Antecedentes. Existe una epidemia de enfermedad renal en la etnia Zuni. En colaboración con los proveedores de salud y con centros de investigación, el Pueblo Zuni estableció el Proyecto Renal Zuni (PRZ), con el objetivo de disminuir la prevalencia de la enfermedad renal.

Métodos. El PRZ condujo un estudio transversal para estimar la prevalencia de albuminuria, hematuria y los factores de riesgo asociados a enfermedad renal en esta población. Los participantes llenaron un cuestionario, aportaron muestras de sangre y orina y registraron su peso, estatura y presión arterial. La encuesta aportó las bases para estudios concurrentes encaminados a identificar factores de riesgo genéticos y ambientales que influyen en la susceptibilidad y avance de la enfermedad renal.

Resultados. La distribución por edad y sexo en el grupo de estudio fue similar a la de la población Zuni elegible. La prevalencia de albuminuria incipiente (AI) (0.03 ≤ razón albumina:creatinina urinaria, RACR < 0.3) y albuminuria franca (AF) (RACR ≥ 0.3) fueron más altas en los diabéticos [AI: 34.3% (28.3, 40.4%); AF: 18.6% (13.7, 23.6%) que en los no diabéticos [AI: 11.1% (9.3, 12.8%); AF: 1.7%, (1.0, 2.5%)]. Los no diabéticos representaron el 58.6% (52.2, 65.0%) y el 30.9% (19.9, 41.9%) de los participantes con AI y AF, respectivamente. La prevalencia de hematuria fue más alta entre los diabéticos [≥ trazas: 47.0% (40.7, 53.4%) ≥ 50 eritrocitos/μL: 25.8% (20.3, 31.4%)] que entre los no diabéticos [≥ trazas: 31.1% (28.5, 33.7%) ≥ 50 eritrocitos/μL: 16.6% (14.5, 18.7%)]. La hipertensión se asoció con albuminuria en ambos grupos. Hipercolesterolemia se asoció con albuminuria entre los participantes no diabéticos. Tanto diabetes como la ingesta de alcohol se asociaron con hematuria.

Conclusion. Tanto la elevada prevalencia de albuminuria entre los no diabéticos, como la de hematuria entre diabéticos y no diabéticos, son consistentes con las altas tasas de enfermedad renal no diabética observadas entre la población diabética y no diabética de la etnia Zuni.

Key words: albuminuria, proteinuria, hematuria, American Indians, diabetic and nondiabetic kidney disease, risk factors, obesity, hypertension, hypercholesterolemia, epidemiology.

Similar to other disadvantaged minorities, American Indians have a disproportionate burden of kidney disease [1]. The prevalence of albuminuria among

American Indians is higher than in the U.S. population [2–4]. In the Strong Heart Study, the prevalence of albuminuria among American Indians aged 45 to 74 years in Arizona (49.8%), Oklahoma (21.3%), and the Dakotas (19.3%) was higher than that in the general U.S. population (11.1%). The age- and gender-adjusted prevalence of end-stage renal disease among American Indians [3552 per million population (pmp)] approaches that among African Americans (4368 pmp) [1] and is 3.7-fold higher than that among European Americans (970 pmp) [1]. Among individuals with albuminuria, the risk for cardiovascular disease exceeds that for end-stage renal disease. Thus, there is an urgent need for community-based screening and the development of primary and secondary prevention programs.

This paper describes how the Zuni Pueblo, located in an isolated rural portion of New Mexico (NM), responded to an epidemic of kidney disease. The Pueblo formed broad-based collaborations with health care providers (Indian Health Service, Dialysis Clinic, Inc.) and research institutions [University of New Mexico (UNM), Southwest Foundation for Biomedical Research] to establish the Zuni Kidney Project (ZKP) and reduce the burden of kidney disease.

In 2000, the age- and gender-adjusted prevalence of end-stage renal disease (ESRD) in Zuni [17,400 per million population (pmp)] was 18.5- and 4.1-fold higher than that among European Americans and African Americans, respectively, and 5.3-fold higher than the composite American Indian rate [1, 5]. Previous studies indicated that high rates of diabetic and nondiabetic kidney disease may contribute to this epidemic [6, 7]. However, these studies were not population-based and may have contained significant selection bias.

The ZKP recognized the need to precisely estimate the prevalence of kidney disease and related risk factors. Thus, it conducted a population-based cross-sectional survey of the Zuni Pueblo [5]. The ZKP is presently conducting additional studies to identify genetic and environmental risk factors for the development and progression of kidney disease and cardiovascular diseases. Specifically, the ZKP is collaborating with UNM's Center for Environmental Health (funded by the National Institute of Environmental Health Sciences) to identify environmental and vocational factors associated with kidney disease. It is also participating in a National Institutes of Health-funded consortium, Family Investigation of Nephropathy and Diabetes, charged with identifying genes that increase susceptibility to diabetic nephropathy and retinopathy [8]. The ZKP also is conducting a National Institutes of Health-funded study of extended families to identify susceptibility genes for diabetic and nondiabetic kidney disease and intermediate phenotypes.

STUDY POPULATION AND METHODS

Approximately 80% of all Zuni Indians live in the Zuni Pueblo, located in McKinley County, NM [9]. There are more than 2000 households and 10,000 tribal members in the pueblo [9]. The median age is 26 years, and only 8% of the population is aged ≥60 years [9]. Ninety percent of the residents speak the Zuni language (Shiwi) [10]. The majority (59%) of adults have graduated from high school [10]. Major occupations include jewelry making, farming, sheepherding, and government jobs.

Community involvement is essential to the success of the ZKP. Tribal members, fluent in both Shiwi and English, were trained as recruiters. The study coordinator (A. B.) was a well-respected Zuni educator. Tribal leaders and community elders had continuing input into study goals and design. Focus groups were held to define specific aims, identify the most efficient methodology, and develop research instruments. A community-wide education program, including age-appropriate education materials, school meetings, childcare centers, community health fairs, radio programs, and newspaper articles, was developed to maximize participation.

The survey was conducted from February 1999 to April 2002 [5]. All Zuni Indians ≥5 years of age ($N = 9228$) [9] were eligible to participate. We used a household sampling frame within neighborhood clusters to maximize participation and reduce differential-surveillance bias. The UNM Human Research Review Committee, the Indian Health Service Institutional Review Board, and the Zuni Tribal Council approved the study. A questionnaire with sections on demographics, medical history, social history, risk factors, and family structure was administered [5]. The reliability and validity of the instrument have been demonstrated [5]. Participants donated blood and urine samples and had blood pressure (BP), height, and weight measured. Serum glucose, total cholesterol, glycosylated hemoglobin (HbA_{1c}), and urine creatinine were measured [5]. Urine albumin was assayed in spot-urine specimens by rate nephelometry, and expressed as urine albumin to creatinine ratio (UACR) [11].

Albumin excretion was classified as normal (UACR <0.03), incipient (IA) (0.03≤UACR <0.3), or overt (OA) (UACR ≥0.3) [11]. Participants were classified as diabetic if they had a prior history of diabetes, random glucose ≥200 mg/dL, or HbA_{1c} >7.0% [11]. Participants with HbA_{1c} between 6.0% and 7.0%, a random glucose <200 mg/dL, and no prior history of diabetes were classified as having an "indeterminate" diabetes status. Assessing the prevalence of albuminuria and hematuria in both the diabetic and indeterminate groups enabled us to obtain conservative prevalence estimates among participants with a low probability of diabetes [12]. Participants aged ≥20 years were classified as overweight if their body

Table 1. Prevalence[a] (%) of incipient and overt albuminuria, hematuria ≥ trace and ≥50 RBC/μL, overweight, obesity, hypertension, and hypercholesterolemia, stratified by sex and diabetes status, among ZKP participants

	Participants without diabetes ($N = 1202$)		Participants with diabetes ($N = 236$)	
	F ($N = 578$)	M ($N = 624$)	F ($N = 162$)	M ($N = 74$)
Incipient albuminuria	9.2[f] (6.8, 11.5)	12.8[b,f] (10.2, 15.4)	32.7 (25.5, 39.9)	37.8 (26.8, 48.9)
Overt albuminuria	1.2[f] (0.3, 2.1)	2.2[f] (1.1, 3.4)	17.9 (12.0, 23.8)	20.3 (11.1, 29.4)
Hematuria ≥ trace	39.8 (35.8, 43.8)	23.1[c,f] (19.8, 26.4)	47.5 (39.8, 55.2)	45.9 (34.6, 57.3)
Hematuria ≥50 RBC/μL	24.9 (21.4, 28.4)	9.0[c,g] (6.7, 11.2)	27.2 (20.3, 34.0)	23.0 (13.4, 32.6)
Overweight	34.1 (30.2, 38.0)	26.4[d,g] (22.9, 29.9)	40.6 (33.0, 48.2)	45.2 (33.8, 56.6)
Obesity	30.6[g] (26.8, 34.4)	19.6[c] (16.5, 22.8)	45.0 (37.3, 52.7)	27.4[d] (17.2, 37.6)
Hypertension	18.7[f] (15.5, 21.9)	31.1[c,f] (27.5, 34.8)	49.4 (41.5, 57.2)	71.4[c] (60.8, 82.0)
Hypercholesterolemia	27.4[f] (21.2, 28.3)	36.9[c] (33.1, 40.6)	39.5 (32.0, 47.0)	40.5 (29.4, 51.7)

Abbreviations are: ZKP, Zuni Kidney Project; F, females; M, males; RBC, red blood cell; incipient albuminuria, urine albumin:creatinine ratio ≥0.03 and <0.3; overt albuminuria = urine albumin:creatinine ratio ≥0.3; overweight, body mass index ≥85th and <95th percentile if aged <20 years, body mass index ≥25 and <30 if aged ≥20 years; obesity, body mass index ≥95th percentile if aged <20 years, body mass index ≥30 if aged ≥20 years; hypertension, prior history of hypertension or systolic or diastolic blood pressure ≥95th percentile if aged <18 years, prior history of hypertension or systolic or diastolic blood pressure ≥140 or ≥90 mm Hg, respectively, if aged ≥18 years; hypercholesterolemia, total serum cholesterol ≥170 mg/dL if aged <20 years, total serum cholesterol ≥200 mg/dL if aged ≥20 years. 95% CI is reported in parentheses.

[a]Variance estimates are adjusted for dependencies created by sampling within families.

[b]$P<0.05$; [c]$P<0.001$; [d]$P<0.01$ for comparison between females and males.

[e]$P<0.05$; [f]$P<0.001$; [g]$P<0.01$ for comparison between diabetes status, within gender.

mass index (BMI) was ≥25 and <30, and obese if BMI ≥30 [11]. Participants aged 5 to 19 years were classified as overweight if their BMI was between the 85th and 94th percentiles, and obese if BMI was at or above the 95th percentile [11]. Participants aged ≥18 years were classified as hypertensive if they had a prior history of hypertension, or had systolic or diastolic BP ≥140 or ≥90 mm Hg, respectively [11]. Participants <18 years of age were classified as hypertensive if they had a prior history or had systolic or diastolic BP ≥95th percentile for age and height [11]. Among participants aged <20 years and ≥20 years, hypercholesterolemia was defined as total cholesterol ≥170 or ≥200 mg/dL, respectively [11]. Alcohol use was defined as a self-report of any alcohol consumption for a duration >10 years.

Statistical analysis

Prevalence of albuminuria and hematuria, and risk factors were expressed as percentages with 95% confidence intervals. Estimates of the variances and covariances were obtained using Taylor series linearization. We used multivariate generalized estimating equations to test for associations of putative risk factors with albuminuria and hematuria among participants aged ≥20 years. Separate models were constructed for diabetic and nondiabetic participants. All models included adjustments for age and gender and controlled for dependencies created by the sampling design. The level of statistical significance was $P<0.05$.

RESULTS

Study sample

Women comprised 51.7% (95% CI 49.2, 54.2) of study participants ($N = 1510$) and 51.9% of the eligible Zuni Tribal Population (ZTP). The proportion of people aged ≥40 years was similar among participants [28.3% (26.1, 30.6)] and the ZTP (29.5%). Among those aged ≥25 years, high school graduates comprised 62.3% (59.1, 65.5) of participants versus 58.7% of the ZTP. Although the study sample appeared to be representative of the ZTP, unidentified sources of bias cannot be excluded.

Diabetes

Among participants aged ≥5 years, the prevalence of diabetes was 15.6% (13.8, 17.5). The prevalence of diabetes was higher among women [20.7% (17.9, 23.6)] than men [10.2% (8.0, 12.3)] ($P<0.001$). Only 4.8% (3.7, 5.8) of participants had an indeterminate diabetes status.

Albuminuria

Prevalence estimates of IA and OA were higher among diabetic than nondiabetic participants ($P<0.001$) (Table 1). The proportion of nondiabetic participants among those with IA and OA were 58.6% (52.2, 65.0) and 30.9% (19.9, 41.9), respectively. Among all participants with UACR ≥0.03, 52.2% (46.5, 57.9) were nondiabetics, 42.4% (36.7, 48.0) were diabetics, and 5.4% (2.8, 8.0) had an indeterminate diabetes status.

Hematuria

The prevalence estimates of hematuria ≥ trace and ≥50 red blood cell/μL were both higher among diabetic than nondiabetic participants ($P<0.01$ and $P<0.001$, respectively) (Table 1). Among nondiabetic participants, the prevalence of hematuria was higher among women than men ($P<0.001$). The prevalence of hematuria was similar among male and female diabetic participants. Among participants with hematuria ≥ trace, 21.7% (18.1,

Table 2. Odds ratios for IA and OA and hematuria ≥ trace, adjusted for age and gender, among survey participants aged ≥20 years, stratified by diabetes status (multivariate model)

	Participants with diabetes ($N = 203$)				Participants without diabetes ($N = 714$)			
Risk factor	IA	OA	IA and OA combined	Hematuria ≥ trace	IA	OA	IA and OA combined	Hematuria ≥ trace
Overweight	0.7 (0.3, 1.6)	0.5 (0.1, 1.8)	0.7 (0.3, 1.6)	1.0 (0.4, 2.5)	1.9[a] (1.1, 3.4)	0.7 (0.2, 2.4)	1.6 (0.9, 2.7)	0.7 (0.5, 1.1)
Obesity	0.7 (0.3, 1.7)	0.9 (0.2, 3.3)	0.8 (0.3, 2.0)	1.2 (0.4, 3.1)	1.8 (0.9, 3.3)	1.1 (0.3, 4.2)	1.6 (0.9, 2.8)	1.4 (0.9, 2.0)
Hypertension	0.9 (0.5, 1.6)	4.2[b] (1.4, 12.4)	1.3 (0.7, 2.4)	1.6 (0.8, 2.9)	3.9[c] (2.4, 6.3)	2.0 (0.7, 5.6)	3.5[c] (2.3, 5.5)	0.9 (0.6, 1.3)
Hypercholesterolemia	1.7 (0.9, 3.3)	2.1 (0.9, 5.2)	1.8 (0.9, 3.3)	0.7 (0.4, 1.3)	2.2[c] (1.4, 3.5)	2.7[a] (1.0, 7.2)	2.3[c] (1.5, 3.6)	1.0 (0.7, 1.5)
Alcohol use (>10 years)	2.2[a] (1.0, 4.8)	1.7 (0.6, 4.8)	2.2[a] (1.1, 4.4)	2.4[a] (1.2, 4.7)	1.7[a] (1.0, 2.9)	2.7 (0.9, 8.3)	1.8[a] (1.1, 3.0)	1.3 (0.9, 2.0)

Abbreviations are: IA, incipient albuminuria; OA, overt albuminuria; incipient albuminuria, urine albumin:creatinine ratio ≥0.03 and <0.3; overt albuminuria, urine albumin:creatinine ratio ≥0.3; overweight, body mass index ≥25 and <30, obesity, body mass index ≥30; hypertension, prior history of hypertension or systolic or diastolic blood pressure ≥140 or ≥90 mm Hg, respectively; hypercholesterolemia, total serum cholesterol ≥200 mg/dL. 95% CI is reported in parentheses.
[a] $P<0.05$; [b] $P<0.01$; [c] $P<0.001$.

25.3) were diabetic, 73.2% (69.3, 77.0) were nondiabetic, and 5.1% (3.2, 7.0) had an indeterminate diabetes status. Among those with hematuria ≥50 red blood cell/μL, 22.4% (17.5, 27.4) were diabetic, 73.5% (68.3, 73.8) were nondiabetic, and 4.0% (1.7, 6.4) had an indeterminate diabetes status.

Overweight, obesity, hypertension, and hypercholesterolemia

Diabetic participants were more likely to be overweight than were nondiabetic participants ($P < 0.01$) (Table 1). Among nondiabetic participants, being overweight was more common among women than men ($P < 0.01$). The prevalence of obesity was higher among diabetic than nondiabetic participants ($P < 0.01$). Among both diabetic and nondiabetic participants, women were more likely to be obese than men ($P < 0.01$). Hypertension was more common among diabetic than nondiabetic participants ($P < 0.001$) and among men than women ($P < 0.001$). Among nondiabetic participants, hypercholesterolemia was more common among men than women ($P < 0.001$).

Risk factors for albuminuria and hematuria

Diabetes was associated with albuminuria and hematuria (Table 2). Hypertension was associated with albuminuria among both diabetic and nondiabetic participants. Hypercholesterolemia was associated with albuminuria among nondiabetic but not diabetic participants. Alcohol use (>10 years) was associated with albuminuria among diabetic and nondiabetic participants and with hematuria among nondiabetic participants.

DISCUSSION

The Zuni Pueblo, recognizing the threat to the community posed by the epidemic kidney disease, established the ZKP. Broad-based community support enabled the ZKP to recruit a representative sample of the Zuni Pueblo. The survey provided evidence that diabetes, hypertension, and alcohol were significant risk factors for albuminuria, and that alcohol use was a risk factor for hematuria among nondiabetic participants.

The prevalence of albuminuria among nondiabetic participants was one of the highest reported among nondiabetic American Indians [13]. The prevalence of hematuria was higher than that observed among the Navajo Indians [14]. The high rates of albuminuria among nondiabetic participants and of hematuria among both diabetic and nondiabetic participants support the hypothesis that nondiabetic kidney disease is common among both diabetic and nondiabetic Zuni Indians. Mesanagiopathic glomerulonephritis, frequently with glomerular deposition of immunoglobulin A, focal sclerosing glomerulonephritis, membranous glomerulopathy, and amyloidosis have been observed on kidney biopsies obtained from Zuni Indians [15, 16].

The causes of the high rates of kidney disease are not readily apparent. The prevalence of diabetes among the Zuni Indians is higher than that in the United States population and the composite American Indian rate [17]. Zuni Indians with diabetes may be at higher risk for diabetic and nondiabetic kidney disease compared with other diabetic American Indians. The observed associations of hypertension with albuminuria are in concert with a report by Hoehner et al [13]. The association of hypercholesterolemia with albuminuria among nondiabetic patients is in concert with epidemiologic [18] and experimental [19] studies, suggesting that hypercholesterolemia

may be a risk factor for susceptibility to and progression of kidney disease. However, the cross-sectional design of our study precluded us from determining if hypercholesterolemia preceded the onset of kidney disease. Similar to the results of previous studies in American Indians [3, 20], we did not demonstrate an independent association between obesity and kidney disease. Among some nondiabetic participants, albuminuria may be attributable to the metabolic syndrome (syndrome X) [21]. An association of albuminuria with the metabolic syndrome has been observed in an Australian Aboriginal community [22].

It is unlikely that traditional risk factors entirely account for the excess burden of kidney disease among the Zuni Indians. Thus, the ZKP is exploring the role of genetic and environmental factors. Among the Zuni Indians, there is familial aggregation of diabetic and nondiabetic kidney disease [15]. An apparent autosomal-dominant mode of inheritance has been reported for immunoglobulin A nephropathy in a Zuni pedigree [23]. The ZKP is currently conducting studies to identify susceptibility genes for diabetic and nondiabetic kidney disease and intermediate phenotypes.

The present study has several unique strengths: (*1*) it was population-based and used a sensitive method for the measurement of albuminuria; (*2*) it obtained precise estimates of putative risk factors for albuminuria; and (*3*) it tested for associations of these risk factors with albuminuria and hematuria among diabetic and nondiabetic participants. The study design enhanced economy and recruitment but imposed significant limitations: (*1*) the use of a single UACR determination may have led to the misclassification of some participants; (*2*) the measurement of UACR, irrespective of medications, including those known to significantly reduce proteinuria, may have led to underestimation of the prevalence of albuminuria; and (*3*) absence of formal glucose tolerance testing prevented detection of individuals with impaired glucose tolerance and albuminuria [3, 24].

The ZKP increased awareness of kidney disease in the community through educational programs delivered with the support of tribal leaders and local health care providers. The ZKP provided an ongoing opportunity to train tribal members in research methodology, with the goal of empowering the community to conduct independent health outcomes research. The ZKP has created the infrastructure for future renal research to assess the role of genetic, environmental, and genetic-environmental interactions in the onset and progression of kidney disease among the Zuni Indians.

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