Abstract. There is an epidemic of renal disease among the Zuni Indians. In contrast to most other American-Indian communities, the epidemic of renal disease among the Zuni Indians reflects high rates of diabetic and nondiabetic renal disease. Almost every Zuni Indian has a relative with end-stage renal disease. This epidemic offers a unique opportunity to advance our understanding of the risk factors for the susceptibility and/or progression of renal disease. Thus, Zuni Tribal leaders formed a research partnership with the University of New Mexico Health Sciences Center, Indian Health Service, Southwest Foundation for Biomedical Research and Dialysis Clinic Inc., to establish the Zuni Kidney Project (ZKP). The ZKP conducted a population-based, cross-sectional survey of the Zuni Pueblo. Age and gender distributions among survey participants were similar to those of the eligible Zuni population. Among diabetics the prevalence (95% confidence interval) of incipient albuminuria (IA) was 32.3% (25.1, 39.5) in women and 36.1% (24.7, 47.5) in men. The prevalence of IA among nondiabetes was 9.3% (6.9, 11.7) in women and 12.2% (9.7, 14.7) in men. Among diabetics, the prevalence of overt albuminuria (OA) was 17.7% (11.9, 23.5) in women and 20.8% (11.4, 30.2) in men. Among nondiabetics, OA was present in 1.2% (0.3, 2.1) of women and 2.3% (1.1, 3.5) of men. Although IA and OA were each more common among diabetics, the majority of participants with albuminuria were nondiabetics. Hematuria was common among both diabetics and nondiabetics. Among diabetics, the crude prevalence of hematuria was similar among men and women. Among nondiabetics, however, hematuria was more common among women. Diabetes and obesity were more common among women than men. In contrast, hypertension and hypercholesterolemia were more common among men than women. The ZKP is incorporating these preliminary data into planning for the development and implementation of primary and secondary prevention programs.

In the United States, minorities carry a disproportionate burden of renal disease. In 2000, point prevalence (per million population [pmp]) of ESRD, adjusted for age and gender, was higher in African- (4240 pmp) and Native Americans (3287 pmp) than in European Americans (943 pmp) (1). The higher prevalences among African Americans and Native Americans, compared with European Americans, reflect higher incidence rates and longer survival. The prevalence of ESRD, adjusted for age and gender, among the Zuni Indians is 17,400 pmp (2). This is 4.1- and 18.5-fold higher than that of African and European Americans, respectively. Moreover, the prevalence of ESRD among the Zuni Indians is 5.3-fold higher than that in the composite Native-American population (1).

The causes of renal disease vary significantly among American-Indian tribes (3). The prevalence of type 2 diabetes mellitus is very high among American Indians. In most American-Indian communities, the vast majority of renal disease is attributable to diabetes. The Pima Indians are experiencing a well recognized epidemic of renal disease due to diabetic nephropathy (4). It is less widely appreciated that the Zuni Indians are also experiencing an epidemic of renal disease. In contrast to the Pima Indians, the epidemic of renal disease among the Zuni Indians reflects high rates of both diabetic and nondiabetic renal disease. The latter is most commonly a mesangiopathic glomerulopathy (Mes GN) (5), often IgA nephropathy. Pasinski and Pasinski reported that between 1973 and 1983, chronic glomerulonephritis and diabetic nephropathy, respectively, accounted for 40% and 24% of ESRD among the Zuni (6). Hoy et al. (7) and Hughson et al. (8) reported that a high proportion of renal biopsy specimens from Zuni Indians showed Mes GN, which was frequently associated with IgA positivity on
immunofluorescence and electron dense deposits on electron microscopy.

**Material and Methods**

**Study Population**

The Zuni Pueblo is located in a rural portion of western New Mexico. The Zuni Indians have lived in the present Pueblo for almost 400 yr. They differ genetically and culturally from the Navajos and other American-Indian tribes. Low rates of emigration and immigration indicate that the community has been relatively endogamous. The 2000 Tribal Census recorded over 2000 households and 10,228 members (9). The median age was 26 yr. Only 8% of the population was over 60 yr of age. The community retains a strong traditional component. Ninety percent of residents speak the Zuni language. The community is economically disadvantaged and approximately half the population lives below the poverty line. The economy is heavily dependent upon jewelry making and other artistic crafts. However, the community established the infrastructure (e.g., electricity, water, and sewer-systems) necessary to maintain public health.

**Establishment of the Zuni Kidney Project**

Almost every Zuni Indian has a relative with ESRD. This led to broad-based community support for renal research on primary and secondary prevention. The Zuni tribal leaders recognized that an innovative approach was necessary to obtain the information necessary to design and implement effective primary and secondary prevention programs. Thus, they established collaborative research partnerships with the Indian Health Service (IHS), University of New Mexico Health Sciences Center (UNMHS), Southwest Foundation for Biomedical Research (SFBR), Dialysis Clinic Inc. (DCI), and National Institutes of Health (NIH). These collaborations culminated in the establishment of the Zuni Kidney Project (ZKP). The ZKP is currently exploring the hypothesis that both genetic and environmental factors modulate the risk for susceptibility and/or progression of diabetic and nondiabetic renal disease. The results of this research will be incorporated into the planning of primary and secondary prevention strategies.

The specific aims of the ZKP are to: (1) educate the community about kidney disease; (2) conduct a population-based, cross-sectional survey (PBCSS) to obtain precise estimates of the prevalence of kidney disease and putative risk factors; (3) conduct a case-control study to identify environmental and vocational risk factors for kidney disease; (4) conduct longitudinal studies of cohorts with normal, incipient, and overt albuminuria defined by urinary albumin creatinine ratio (UACR) expressed as true ratio; (5) conduct a study of extended Zuni families to identify risk factors for renal disease and intermediate phenotypes; and (6) develop strategies to prevent the occurrence and progression of renal disease. This paper describes the development of the ZKP, educational programs, methodology, and preliminary results from the PBCSS, and plans for the development and implementation of primary and secondary prevention programs.

The UNMHS Human Research Review Committee, IHS Institutional Review Board, and the Zuni Tribal Council approved the project. Informed consent was obtained from each adult participant and from a parent or legal guardian for each participant less than 18 yr of age. The Zuni language is not a written language, so the consent form was written in English. Study staff translated the consent form verbally for those tribal members who could not read English.

**Education**

Because the ZKP grew from the community’s vision of a unique research partnership, we developed effective programs to educate the community about the diagnosis, treatment, and prevention of kidney disease. The project’s study coordinator (AB) is a professional educator, who previously served the community as the director of the science curriculum for the Zuni public schools. Under her leadership, the ZKP developed a wide variety of educational programs. These programs used different venues to disseminate information, including school programs, community health fairs, public service announcements on the local radio station, and articles in the Shiwi Messenger, the pueblo’s local newspaper. These efforts heightened community awareness and stimulated interest in acquiring additional information about kidney disease. Many tribal members visited the ZKP office to talk with project staff and to acquire additional printed educational material.

**Population-Based Cross-Sectional Survey (PBCSS)**

The PBCSS is the foundation of the ZKP. The specific aims of the PBCSS include to: (1) estimate the prevalence of renal disease; (2) assess potential risk factors for renal disease; and (3) identify participants for planned case-control, longitudinal-cohort, and family studies to identify environmental, familial, and genetic risk factors for the susceptibility and/or progression of renal disease. All residents ≥5 yr of age were eligible for participation in the PBCSS. The ZKP recognized the importance of random selection of participants. However, random sampling of individuals was not feasible. The Zuni Tribal

### Table 1. Prevalence (%) of incipient and overt albuminuria, stratified by age, gender, and diabetes

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Incipient</th>
<th>Overt</th>
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<tbody>
<tr>
<td></td>
<td>F</td>
<td>M</td>
</tr>
<tr>
<td>5 to 39</td>
<td>32.4 (16.6, 48.1)</td>
<td>26.1 (6.1, 46.1)</td>
</tr>
<tr>
<td>≥40</td>
<td>32.3 (24.4, 40.2)</td>
<td>40.8 (27.1, 54.6)</td>
</tr>
<tr>
<td>All</td>
<td>32.3 (25.1, 39.5)</td>
<td>36.1 (24.7, 47.5)</td>
</tr>
<tr>
<td>Participants without diabetes (female participants = 570; male participants = 607)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 to 39</td>
<td>8.2 (5.6, 10.7)</td>
<td>11.4 (8.7, 14.1)</td>
</tr>
<tr>
<td>≥40</td>
<td>13.7 (7.4, 19.9)</td>
<td>16.9 (9.1, 24.7)</td>
</tr>
<tr>
<td>All</td>
<td>9.3 (6.9, 11.7)</td>
<td>12.2 (9.7, 14.7)</td>
</tr>
</tbody>
</table>

*F = female participants; M = male participants. Albuminuria was classified according to ADA guidelines as normal (UACR < 0.03), incipient (0.03 ≤ UACR < 0.3), or overt (≥0.3) (12). 95% Confidence interval are reported in brackets.*
Table 2. Age-adjusted prevalence (%) of overweight, obesity, high cholesterol, and hypertension, stratified by age and gender a

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Female</th>
<th>Male</th>
<th>Female</th>
<th>Male</th>
<th>Female</th>
<th>Male</th>
<th>Female</th>
<th>Male</th>
<th>Female</th>
<th>Male</th>
<th>Female</th>
<th>Male</th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>19.1 a [16.4, 21.9]</td>
<td>11.6 [9.0, 14.2]</td>
<td>33.5 [30.0, 37.0]</td>
<td>29.1 [25.6, 32.6]</td>
<td>34.3 a [30.8, 37.7]</td>
<td>21.4 [18.2, 24.5]</td>
<td>34.3 [30.8, 37.7]</td>
<td>36.3 [32.6, 40.0]</td>
<td>25.8 b [22.6, 29.0]</td>
<td>36.5 [32.7, 40.2]</td>
<td>25.8 b [22.6, 29.0]</td>
<td>36.5 [32.7, 40.2]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a F/H11005/n female Zuni Indians; M/H11005/male Zuni Indians. Diabetes: prior history of diabetes, or random glucose ≥200 mg/dl (14), or HbA1c ≥7.0% (11).

Overweight: participants over 20 y of age: BMI ≥25 and <30; participants 5 to 19 y of age: BMI ≥85th and <95th percentile. Obesity: participants ≥20 y of age BMI ≥30; participants 5 to 19 y of age: BMI ≥95th percentile for age and height obtained from gender-specific charts. High cholesterol: participants over 20 y of age total serum cholesterol <170 mg/dl; participants 5 to 19 y of age total serum cholesterol <200 mg/dl. Hypertension: systolic or diastolic BP ≥140 mm Hg, or diastolic BP ≥90 mm Hg.

Data Management

All data obtained from the PBCSS were entered into an ACCESS (Microsoft, Seattle, WA) database. To monitor contacts with community members, a tracking system was developed. Households were assigned a unique identifier. All contact dates, names of participants and canvassers, and results of each visit were recorded. We recorded laboratory reference numbers and dates for enrollment, procurement of laboratory samples, notification of participants of results, and physician referrals. Tracking reports checked the accuracy of questionnaires and laboratory samples. The data management system had restricted user access.

Statistical Analysis

Data were analyzed using SAS (SAS Institute, Cary, NC) and SUDAAN (RTI, Research Triangle Park, NC). Standard statistical methods were not appropriate due to the complex sampling scheme. SUDAAN, a statistical software package for analysis of complex samples, and SAS were used to obtain prevalence estimates and standard errors. SAS was also used to fit generalized estimating equations to model disease status. These models can be considered an extension of logistic regression models that accommodate the sampling procedure. Prevalences of selected variables were age- and gender-adjusted to the 2000 Zuni Tribal Census (9).

PBCSS Questionnaire

A questionnaire, based on the Behavioral Risk Factor Surveillance Survey and the Strong Heart Study questionnaires (2), was developed to obtain information pertinent to renal disease and related risk factors. The instrument was refined through discussions with the tribal leadership and the community to ensure compliance with Zuni social norms and cultural customs. The questionnaire contains sections on household, demographics, medical and physical history, social history, and exposure to potential risk factors (tobacco use, lack of exercise, alcohol consumption, drinking water supply, nonalcoholic drinks), family structure, and health history. Reproducibility and validity of the questionnaire were established by assessing responses on duplicate administrations and comparing responses with medical records, respectively.

Classification of Participants

To control costs, enhance efficiency, and maximize recruitment, we used recently validated epidemiologic screening tools (e.g., single
spot urine samples for UACR and HbA1c to screen for diabetes) (10–11). Albuminuria was classified according to American Diabetes Association (ADA) guidelines as normal (UACR < 0.3), incipient (IA) (0.33 ≤ UACR < 0.3), or overt (OA) (≥0.33) (12). We considered using UACR gender-specific cut-points (13). However, among ZKP participants, the ratio of the mean urinary creatinine for women to men was 0.90. Thus, we classified participants according to the ADA guidelines (12), which do not recommend gender-specific cut-points. Participants were classified as diabetic if they had a prior history of diabetes, a random glucose ≥200 mg/dl (14), or HbA1c >7.0% (11). Participants above 20 yr of age were classified as overweight if their body mass index (BMI) was ≥25 and <30, and as obese if BMI ≥30 (15). Among participants 5 to 19 yr of age, BMI percentiles were obtained from gender-specific growth charts (16). Participants were classified as overweight if their BMI was ≥ the 85th and <95th percentiles and obese if their BMI was ≥95th percentile (17). Participants ≥18 yr of age were classified as hypertensive if they had a prior history of hypertension, a systolic BP ≥140 mmHg, or a diastolic BP ≥90 mmHg (18). Children (<18 yr) were classified as hypertensive if they had a prior history of hypertension, or had systolic or diastolic BP ≥95th percentile for age and height obtained from gender-specific charts (19). Hypercholesterolemia was defined as a total serum cholesterol ≥170 mg/dl and ≥200 mg/dl for those <20 and ≥20 yr of age, respectively.

Results

The preliminary results presented here are based on participants enrolled in the PBCSS. We compared the demographics of participants to the Zuni population using the 1990 (20) and 2000 censuses (9). The sample and the censuses were similar with respect to gender, age, and education, indicating that study participants were likely representative of the eligible population (2). The prevalence of albuminuria among survey participants, stratified by age, gender, and diabetes status, is shown in Table 1. The prevalence (95% confidence interval) of IA among diabetics was 32.3% (25.1, 39.5) in female and 36.1% (24.7, 47.5) in male participants. The prevalence of IA among nondiabetics was 9.3% (6.9, 11.7) in women and 12.2% (9.7, 14.7) in male participants. The prevalence of OA was also higher among diabetics than nondiabetics. Although the prevalence of albuminuria was higher among diabetics versus nondiabetics, the majority of participants with albuminuria were nondiabetics.

The prevalences of putative risk factors for albuminuria (e.g., overweight, obesity, high cholesterol, and hypertension stratified by age and gender) are shown in Table 2. Both diabetes and obesity were more common among female than male Zuni Indians. In contrast, hypertension and hypercholesterolemia were more common among male Zuni Indians.

The crude prevalence of hematuria (dipstick ≥ trace), stratified by age, gender, and diabetes, is shown (Table 3). Hematuria was common among both diabetics and nondiabetics. Among diabetics, the crude prevalence of hematuria was similar in male and female participants. Among nondiabetics, however, the crude prevalence of hematuria was higher among female than male participants.

Discussion

The epidemic of renal disease in the Zuni Indians is unique among American-Indian communities because of the high prevalence of nondiabetic renal disease. Specifically, this study demonstrates that the prevalence of albuminuria is higher among diabetics than nondiabetics. However, because the number of nondiabetic participants greatly exceeded the number of diabetic participants, the majority of Zuni Indians with albuminuria did not meet the criteria for type 2 diabetes mellitus. However, because the prevalence of diabetes is very high and increases with advancing age, we anticipate that a significant proportion of nondiabetic participants with albuminuria may eventually develop type 2 diabetes mellitus. Putative risk factors for albuminuria (e.g., diabetes, obesity, and hypertension were common among the Zuni Indians).

In concert with the wishes of the community, renal biopsies were not performed for research purposes during this study. Previous reports have demonstrated that both diabetic nephropathy and Mes GN occur frequently among the Zuni Indians (21). IgA nephropathy is the most common form of Mes GN among the Zuni Indians. Diabetic nephropathy and Mes GN may coexist in the same person (8). The high rates of hematuria observed among diabetics and nondiabetics are consistent with the hypothesis that Mes GN may frequently occur among diabetic and nondiabetic Zuni Indians.

The identification of risk factors and people with incipient renal disease will facilitate the development and implementation of primary and secondary prevention strategies. The education programs will increase the community’s knowledge of renal disease and motivate behaviors to decrease the risk for the development and progression of renal disease. The ZKP will work closely with the Zuni Wellness Program and the Zuni Diabetes Program to reduce the prevalence of diabetes, a major

| Table 3. Prevalence of hematuria (%), stratified by age, gender, and diabetes |
|-----------------------------|-----------------------------|-----------------------------|
| Age (yr) | Participants with Diabetes | Participants without Diabetes |
| | F (n = 161) | M (n = 73) | F (n = 592) | M (n = 630) |
| 5 to 19 | 50.0 (0.0, 100.0) | 0 | 32.6 (25.7, 39.5) | 21.5 (15.5, 27.5) |
| 20 to 39 | 35.5 (18.6, 52.3) | 37.5 (18.5, 56.5) | 42.6 (36.6, 48.5) | 20.6 (15.8, 25.3) |
| 40 to 59 | 49.4 (38.4, 60.4) | 53.3 (35.5, 71.2) | 45.4 (36.3, 54.5) | 37.4 (26.8, 47.9) |
| ≥ 60 | 53.2 (38.9, 67.5) | 50.0 (26.9, 73.1) | 40.0 (18.5, 61.5) | 21.7 (4.9, 38.6) |
| All | 47.8 (39.8, 55.8) | 46.6 (35.2, 58.0) | 40.0 (35.9, 44.1) | 23.2 (19.7, 26.7) |

* F = female participants; M = male participants. Hematuria: dipstick ≥ trace. 95% CI are reported in brackets.
risk factor for renal disease. The ZKP will develop a Hypertension Control Program to decrease the risk for progression of renal disease. The case-control study will allow the identification of vocational and environmental risk factors. This will enable the ZKP to suggest implementation of changes in the work place and home environments to reduce the risk of kidney disease. The planned longitudinal cohort studies will allow the ZKP to identify and modify risk factors for progression and improve secondary prevention programs. The planned study of extended families will identify genetic risk factors. This will facilitate identification of individuals at high risk who can then be targeted for early therapeutic intervention.

Acknowledgments

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