Cardiovascular Disease in Navajo Indians With Type 2 Diabetes

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Synopsis

Rates of both type 2 diabetes and cardiovascular disease have risen sharply in recent years among Navajo Indians, the largest reservation-based American Indian tribe, but the association between the two conditions is not entirely clear.

Rates of cardiovascular disease and some possible associations in several hundred diabetic and nondiabetic Navajos were estimated. Nearly one-third (30.9 percent) of those with diabetes had formal diagnoses of cardiovascular disease—25.3 percent had heart disease, 4.4 percent had cerebrovascular disease, and 4.1 percent had peripheral vascular disease. (The percentages exceed the total because some people had more than one diagnosis.) Age-adjusted rates were 5.2 times those of nondiabetics for heart disease, 10.2 times for cerebrovascular disease, and 6.8 times for peripheral vascular disease.

Accentuation of risk was most marked in young diabetics and in female diabetics. Hypertensive diabetics had a twofold increase in heart disease and more than a fivefold increase in cerebral and peripheral vascular disease over nonhypertensive diabetics. Age, blood pressure, cholesterol levels, and albumenuria were independent risk factors for cardiovascular disease. Triglyceride levels or body weight were not. Male sex and diabetes duration were independent risk factors for cerebral and peripheral vascular disease but not for heart disease.

In view of the impressive segregation of cardiovascular disease in the diabetic Navajo population, the prevention of diabetes through population-based health promotion seems basic to its containment. Over the short term, vigorous treatment of hypertension in subjects who are already diabetic is mandatory.

AMERICAN INDIANS, like many populations in epidemiologic transition, are experiencing increasing rates of obesity, hypertension, and type 2 diabetes that were rare in their forebears (*1–4*). This syndrome is attributed to changes in diet and activity superimposed on a genetic predisposition (*5*). A central role for insulin resistance and hyperinsulinemia has been proposed (*5–12*). It is complicated by renal and cardiovascular disease.

Diseases of the heart are now the leading cause of death for adult Indian men and women nationwide. The age-adjusted death rate in 1986–88 was 171 per 100,000 population, equal to the U.S. total rate, and cerebrovascular disease was the fourth leading cause of death, with a higher rate than the U.S. total—33 per 100,000 versus 30.3 (*13*). Death rates from atherosclerosis and hypertension are approaching the U.S. average—0.6 per 100,000 for atherosclerosis and 0.7 for hypertension in 1987 (*14*). Further increases can be expected as the full susceptibility to this syndrome is expressed, and the youthful Indian population ages (*15*).

There is, however, marked regional variation in rates of cardiovascular disease among Indians (*13,16*). In 1986–89, death rates from heart disease varied threefold, from 99 per 100,000 in the Navajo

'NPPs provide access to care in settings where there is an inadequate supply of physicians and expand the scope of care available to patients by emphasizing services that physicians might not address, . . .'

Area to 288 in the Aberdeen Area (*13*), and cerebrovascular disease death rates varied threefold between the Navajo and Bemidji Areas (19.7 for the Navajos and 55 for the Bemidji (*13*). Differences in diabetes rates account for only some of this variation (*17,18*).

Type 2 diabetes is said to amplify baseline cardiovascular risk in any population by a factor of two to four, with the relative increase most marked in younger people with diabetes and in females (*19–28*). The pathogenesis of cardiac and noncardiac forms of disease probably differs somewhat (*19–22,24,25,29*). Relationships between albumenuria and cardiovascular disease in diabetics suggest a renal-vascular link that has not been fully elucidated (*23,30–35*).

The Navajo Indians, of Athabascan origin, are the largest reservation-based Native American tribe, with an estimated 1992 population of 201,583 (*36,37*). Their annual growth rate is 2.8 percent (*36,38*), and the population is very youthful, with 50.4 percent < age 20 and only 7.2 percent ages 65 and older. Like most tribes, the Navajos have experienced recent increases in body weight, blood pressures, and lipid levels (*1,39–42*), but cigarette smoking is still relatively uncommon (*43,44*). Diabetes, almost unheard of in the 1930s, was diagnosed in 17.2 percent of Navajos ages 20-74 years in one community screening program in 1989–90, an age-adjusted rate 2.5 times the U.S. average (*45,46*).

Although death rates of Navajos from cardiovascular disease are the lowest among Indians nationwide, they are increasing rapidly. Diagnosed myocardial infarctions increased 243 percent among men and 496 percent among women from 1976–79 to 1984–86, with half or more occurring in people with diabetes (*45,47*). Heart disease is now the leading cause of death among Navajos after accidents, with an age-adjusted 1986-88 rate 0.58 times the U.S. average (*13*). Cerebrovascular disease is the seventh most common cause of death, at 0.65 times the U.S. rate (*13*). Amputation rates are rising; two thirds of amputations in the mid 1980s were associated with diabetes (*24,45*), and rates among people with diabetes were at least as common as for U.S. diabetics in general.

In 1990, we established a profile of more than 400 Navajo people with diabetes and compared them with Navajos who did not have diabetes (*48*). In this report, we describe the rates, patterns, and associations of cardiovascular disease in this population.

Methods

In June, July, and August 1990, we gathered data on more than 400 Navajo Indians with type 2 diabetes attending the diabetes clinic at the Indian Health Service (IHS) Hospital in Tuba City, AZ, and on a similar number of Navajos without diabetes attending the medical clinic at the same facility. Type 2 diabetes is diagnosed in IHS by National Diabetes Data Group criteria (*49*), with screening at the annual physical examination recommended for all Indians ages 18 and older.

The first eight people who attended each of the two clinics every day were included until the samples were complete. Those with end stage renal disease (ESRD), whose care is largely rendered in the dialysis unit, were excluded. We recorded sex, birth date, blood pressure, weight, and tribe of each person. We also measured urinary albumen concentration on a random urine specimen by a nephelometric technique, using the Beckman Immunochemistry System (*50–55*). Urinary albumen excretion (UAE) was expressed as milligrams (mg) of albumen per gram (gm) of creatinine, in the categories of probably normal (< 20 mg per gm), microalbumenuria (20–299 mg per gm), indicating mild diabetic nephropathy, and overt albumenuria (≥ 300 mg per gm), indicating established nephropathy (*54*).

We subsequently reviewed every medical record for date of diagnosis of diabetes and for formal diagnoses of hypertension, retinopathy, and neuropathy. Diagnoses or evidence of ischemic, hypertensive, and atherosclerotic cardiac disease (angina, congestive heart failure, myocardial infarction, compatible electrocardiagram changes), of cerebrovascular disease (transient ischemic attacks, strokes), and of peripheral vascular disease (ischemia, claudication, ulcers, gangrene, amputations) were also recorded. Diagnoses of rheumatic or other forms of heart disease were excluded. When available, the patient's height and most recent levels of serum creatinine, cholesterol, and triglycerides were also noted.

Data were entered into an EPI-INFO program, stored in a Microvax computer and analyzed by the Statistical Analysis System. Those with diabetes and those without were grouped by sex into three age

Table 1. Cardiovascular disease rates in Navajo Indians with diabetes

	Percent of diabetics with							
	Cardiac disease		Cerebrovascular disease		Peripheral vascular disease		All forms	
Age (years)	Women	Men	Women	Men	Women	Men	Women	Men
20–30	5.6	4.8	0	0	0	0	5.6	4.8
40–59	20.6	24.4	3.7	6.1	0	6.1	23.4	36.6
⩾ 60	26.1	44.4	2.7	8.3	7.2	5.6	34.2	58.3
All	22.0	29.7	3.0	6.3	3.4	5.1	27.1	41.7
OR (CI) males:females	1.69 (1.1, 2.8)		2.31 (0.8, 6.8)		1.71 (0.6, 5.0)		2.35 (1.5, 3.8)	

NOTE: OR = adjusted odds ratio; CI = 95 percent confidence interval.

Table 2. Accentuated risk for cardiovascular disease in Navajo Indians with diabetes

	Diabetics versus nondiabetics					
	Women		Men		All	
Condition and age	Odds ratio	CI	Odds ratio	CI	Odds ratio	CI
Heart disease, total	5.8	2.3, 16.9	3.6	1.5, 8.8	5.2	2.7, 91.9
20–39 years	6.5	6, 251	1.7	0.2, 25.6	3.2	0.4, 24.6
40–59 years	19.2	2.6, 390	5.5	1.4, 24.7	8.9	3.0, 30.2
⩾ 60 years	2.9	0.9, 10.7	2.5	0.6, 11.7	3.6	1.5, 9.2
Cerebrovascular disease, total	Undefined		5.5	0.7, 110	10.2	1.3, 193
Peripheral vascular disease, total	Undefined		3.8	0.5, 94.6	6.8	1.0, 150
All forms of cardiovascular disease	7.1	2.8, 20.0	5.8	2.5, 12.7	6.5	3.5, 11.6

NOTE: CI = 95 percent confidence interval.

categories: 20–39 years, 40–59 years, and 60 years or older. Proportional data were compared by Mantel Haenzel stratified analysis, with Cornfield 95 percent confidence intervals. Multivariate logistic regression modeling of cardiovascular disease was performed, with a P value <0.2 required for entrance into the model.

Full confidentiality was maintained in the execution of this study and analysis of its results. People are identified only in aggregate and no personal descriptors are used.

Results

We report data on the 411 Navajos with diabetes and the 366 Navajos without diabetes who were ages 20 and older at the time of the screening. The mean and median ages of diabetics and nondiabetics were matched within 2 years in each of the three age groups. The diabetics represented approximately one-third of the estimated 1,200 with diabetes registered in the IHS Tuba City Diabetes Program.

The demographic characteristics of the people with diabetes, their blood pressure and renal profiles, and other clinical features have been described in detail elsewhere (*48,56*). We merely summarize them.

As is the case in other populations of people with type 2 diabetes (*28,46,57,58*), females outnumbered males, in a ratio of 1.35 to 1. Age at screening ranged from 20 to 98 years, with a mean of 56 and median of 58 years.

Age distribution was 20–39 years, 9.7 percent; 40–59 years, 45.9 percent; and 60 years and older, 44.4 percent. Age at diagnosis of diabetes ranged from 15 to 93 years, with a mean of 49.3 and a median of 49.7 years. One quarter of the people had been diagnosed before they were 40 years old, with the following distribution: < 20 years, 1.3 percent; 20–39 years, 23.7 percent; 40–59 years, 55.8 percent; and ⩾ 60 years, 19.3 percent.

Time since diagnosis of diabetes ranged from 0 to 27 years, but it was on average fairly short, as reflected by the mean of 8.0 and median of 6.3 years, and the following distribution: < 5 years, 42.2 percent; 5–9 years, 24.1 percent; 10–14 years, 17.6 percent; and ⩾ 15 years, 17.1 percent. Thus, nearly half had carried the diagnosis for less than 5 years and two-thirds for less than 10 years.

Females with diabetes were on average 122 percent of age and sex-specific ideal body mass index (BMI) and males were 111 percent of ideal BMI; 47 percent of females and 28.3 percent of males were "obese,"

Table 3. Manifestations of cardiovascular disease in Navajo Indians; percentage of affected persons by diagnosis

Type of disease	Percent
Cardiac:	
Arrhythmias, heart block	59.3
Angina	40.9
Myocardial infarction	22.8
Congestive heart failure	13.3
Left ventricular hypertrophy	7.6
Ischemic cardiogram changes only	3.1
Peripheral vascular:	
Foot ulcer(s)	50.0
Gangrene of toes	25.0
Below-knee amputation	12.5
Ischemia of toes	12.5
Cerebrovascular:	
Stroke	69.2
Transient ischemic attacks	23.0
Focal seizures	7.8

defined as ≥ 120 percent of ideal BMI (*59*). Relative overweight became less pronounced with increasing age. More than half the people with diabetes had hypertension by formal diagnosis or treatment, an adjusted rate more than 6 times that of people without diabetes. In addition, blood pressures were elevated at time of screening [≥ 140 millimeters of mercury (mm Hg) or diastolic ≥ 90 mm Hg, or both] in 48.9 percent, indicating suspected or inadequately treated hypertension (*60,61*).

Almost 60 percent of the people with diabetes had at least moderately elevated levels of cholesterol and triglycerides [≥ 200 milligrams per deciliter (mg per dl)]. Hypertension and hyperlipidemia were well established, even in young people with diabetes, and rates in females were comparable to those in males, with reduction in the relative protection evident in females without diabetes.

More than half (54.3 percent) of people with diabetes had elevated albumen excretion, 12.7 percent had overt albumenuria, and 10.6 percent had creatinine levels suggesting renal insufficiency (*62,63*). Retinopathy had been diagnosed in 40.6 percent; 28.4 percent had neuropathy.

A total of 127 people with diabetes had diagnoses of cardiovascular disease; 105 had heart disease, 18 had cerebrovascular disease, and 17 had peripheral vascular disease. Twelve people had disease in more than one system; six had heart and cerebrovascular disease, four had heart and peripheral vascular disease, one had peripheral and cerebral vascular disease, and one man had disease in all systems. In contrast only 16 people without diabetes had cardiovascular disease; 14 had heart disease, one man had cerebrovascular disease, and one man had peripheral vascular disease. No cerebral or peripheral vascular disease was documented in women without diabetes, and none of the nondiabetics had more than one form of cardiovascular disease.

Table 1 shows rates of cardiovascular disease in diabetics by age and sex. Heart disease was present in even the youngest, but it increased with age, affecting, overall, more than a fifth of women and 30 percent of men. Peripheral and cerebrovascular disease were less common and were confined to the middle aged and the elderly with diabetes. About 30 percent of women and 40 percent of men had some manifestation of cardiac or vascular disease. Age-adjusted rates were higher for men than for women.

Table 2 shows the age- and sex-specific estimated increase in risk of diabetics for cardiovascular disease compared with nondiabetics. Heart disease was increased overall more than fivefold, with the greatest increases for women and for middle aged diabetics of both sexes. Cerebrovascular disease was increased tenfold and peripheral vascular disease nearly sevenfold; the absence of these diagnoses in women without diabetes suggests a greater increase in risk for diabetic women than for diabetic men.

Table 3 shows the manifestations of cardiovascular disease. Many people had more than one cardiac manifestation. Claudication was notably absent from the peripheral vascular disease category.

In table 4, diabetics without apparent cardiovascular disease are compared with those who have heart disease only and with those who have peripheral or cerebrovascular disease, or both. Diabetics with cardiovascular disease were more likely than those without cardiovascular disease to be male; they also tended to be older and to have had diabetes longer. They were less likely to be obese, more likely to be under their ideal BMI, and had higher rates of hypertension, retinopathy, neuropathy, overt albumenuria, and suspected renal insufficiency. These trends were more marked in people with cerebrovascular and peripheral vascular disease than in those with heart disease alone. Rates of microalbumenuria and of elevated cholesterol or triglyceride levels did not differ among the groups.

The associations of hypertension with cardiovascular disease manifestations are shown in table 5. Heart disease was present in a considerable proportion of nonhypertensive diabetics, but the rate was doubled in those with hypertension. Cerebral and peripheral vascular disease segregated more strongly in the hypertensive group.

Table 6 shows the association of cardiovascular disease with time since diagnosis of diabetes. Heart disease was evident in almost one fifth of those with diabetes for < 5 years, and rates rose only modestly

Table 4. Associations of cardiovascular disease in Navajos with diabetes

Indicator	Diabetics with—			Significance[1]
	No cardiovascular disease	Heart disease only	Peripheral or cerebrovascular disease, or both	
Male to female ratio	0.6:1	1:1	1.4:1	$P_1 = .018$, $P_2 = .33$
Age, mean years, ± SD	54.8 ± 12.8	61.3 ± 11.3	63.7 ± 10.8	$P_1 < .001$, P_2 = NS
Duration of diabetes, mean years, ± SD	7.3 ± 6.2	9.2 ± 6.3	11.2 ± 4.4	$P_1 < .001$, P_2 = NS
⩾ 120 percent of ideal BMI (percent)	41.0	35.4	21.7	$P_1 = .028$, $P_2 = .07$
< 100 percent of ideal BMI (percent	13.8	21.5	21.7	$P_1 = .017$, P_2 = NS
Hypertension (percent)	51.4	69.2	87.8	$P_1 = <.001$, $P_2 = .043$
Retinopathy (percent)	35.4	44.0	70.0	$P_1 = .009$, $P_2 = .02$
Neuropathy (percent)	25.1	27.6	56.5	$P_1 = .07$, $P_2 = .004$
UAE ⩾ 300 mg per gm (percent)	9.2	17.3	24.0	$P_1 = .006$, $P_2 = .67$
Elevated serum creatinine (percent)	7.9	13.8	18.2	$P_1 = .015$, $P_2 = .6$

[1] P_1 = people with cardiovascular disease versus those with no cardiovascular disease. P_2 = people with heart disease only versus those with cerebrovascular or peripheral vascular disease, or both.

NOTE: SD = standard deviation; BMI = body mass index; UAE = urinary albumen excretion.

thereafter. Cerebral and peripheral vascular disease, however, were uncommon within the first five years of diagnosis and increased more than fivefold with disease of ⩾ 10 years.

Logistic regression analysis showed independent associations of cardiovascular disease with increasing age, with hypertension, cholesterol of ⩾ 200 mg per dl, UAE of ⩾ 300 mg per gm, and male sex. BMI and diabetes length escaped significance ($P = .1$), and triglyceride levels did not enter the model. When modelled separately, however, the associations of heart disease alone, and of cerebral or peripheral vascular disease, or both, differed somewhat.

Heart disease alone was significantly associated with increasing age with a relative risk (RR) for 1 year's increase of 1.04 (1.02–1.07); with UAE ⩾ 300 mg per gm, RR 2.68 (1.18–6.05); with hypertension, RR 2.83 (1.36–5.92); and with cholesterol ⩾ 200 mg per dl, RR 2.35 (1.01–5.48). Sex escaped significance ($P = .078$), and length of diabetes did not enter the model.

Peripheral or cerebrovascular disease, or both, were significantly associated with age, (RR for 1 year's rise 1.13 (1.04–1.23); with UAE ⩾ 300 mg per gm, RR 5.16 (1.47–18.1); with cholesterol ⩾ 200 mg per dl, RR 11.3 (1.64–77.4); with diabetes duration of ⩾ 5 years, RR 7.72 (1.72–34.6); and with male sex, RR 5.5 (1.69–18.0). The extra risk associated with each unit rise in systolic blood pressure was 1.02 (0.98–1.06) and with hypertension 2.87 (0.64–12.88).

Discussion

Some methodologic issues influence the findings in this study. Cardiovascular disease is underestimated by the insensitive method of ascertainment; its full impact is further masked by a survivor effect, and by exclusion of ESRD patients, who have high rates of cardiac and vascular disease (*64*). A cohort effect from changing health patterns among the Navajo confounds interpretation of age-related trends.

'Although death rates of Navajos from cardiovascular disease are the lowest among Indians nationwide, they are increasing rapidly. Diagnosed myocardial infarctions increased 243 percent among men and 496 percent among women from 1976–79 to 1984–86, with half or more occurring in people with diabetes.

The prevalence of cardiovascular disease in Navajo diabetics was striking; nearly a third were afflicted overall. Of those ages 60 and older, who comprise nearly half the diabetic population, one third of the women and nearly 60 percent of the men were afflicted. These rates were not dissimilar to those in Pima and Oklahoma Indian diabetics from 1975 to 1978 (*21*), although our criteria were more inclusive. Rates were somewhat lower than those in Mohawk Indians with diabetes, ascertained in 1985 from medical record review (*27,28*), but their 6.4-fold increase over rates in nondiabetics was identical.

Heart disease was the major cardiovascular morbidity associated with diabetes, as observed by others (*19–23,27,28*), but accentuation of risk over people without diabetes appeared to be greater for cerebral and peripheral vascular disease. Risk enhancement was greater for young and middle aged diabetics, and

Table 5. Hypertension and cardiovascular disease in Navajos with diabetes, by percentage

Type of disease	Nonhypertensive diabetics	Hypertensive diabetics	Hypertensive vs. nonhypertensive RR	CI
Cardiac	16.4	32.0	2.0	1.3, 2.9
Cerebrovascular	1.2	6.6	5.7	1.3, 24.4
Peripheral vascular	1.2	6.2	5.3	1.2, 23.0
All forms	18.7	39.4	2.1	1.5, 2.9

NOTE: RR = Rate ratio, CI = 95 percent confidence interval.

Table 6. Cardiovascular disease in Navajos with diabetes by estimated duration of their diabetes

Condition	Estimated duration of diabetes: < 5 years	5–9 years	≥ 10 years	Significance
Heart disease only	19.3	20.4	27.7	$P = .12$
Cerebral, peripheral vascular, or mixed	2.5	10.7	13.6	$P < .001$
All forms	21.7	31.2	40.0	$P < .001$

for women rather than men. Navajo male diabetics, however, were still more susceptible to cardiovascular disease than women, at variance with Mohawk diabetics and older Pima and Oklahoma Indian data (*21,27,28*) but compatible with cardiographic findings in Pima diabetics (*33*) and with amputation data in several other Indian groups (*24–26,65,66*). Accentuation of cardiovascular disease risk in women diabetics is probably mediated through masculinization of risk factors, including blood pressure and lipid profiles (*22,48*) and has been attributed to the virilizing effect of long-standing insulin resistance that predisposes to the diabetic state (*67*).

The manifestations of cardiovascular disease in this population were not unusual, except for the absence of peripheral claudication. This symptom also was absent in Pima and Oklahoma Indian diabetics in the 1970s, although they had high rates of amputations (*21*). This might be attributed to a methodologic problem or might reflect a relatively greater contribution of microangiopathy or neuropathy, or both, to gangrene and amputations in Indian diabetics.

Our data support somewhat different pathogeneses of heart disease and of cerebral and peripheral vascular disease in people with diabetes. The presence of heart disease in a high proportion of people within the earliest years of recognized diabetes and its independence from diabetes duration suggests that it is generated in the prediabetic state, as others have proposed (*19,8,9,68*), possibly by longstanding insulin resistance or hyperinsulinemia (*6,7,11,12*). In addition, "subhypertensive" diabetics were at considerable risk for heart disease, and male sex was not a strong independent determinant. Cerebral and peripheral vascular disease, on the other hand, retained strong independent associations with male sex and with diabetes duration; the latter supports a specific promoting effect of hyperglycemia.

Although Navajos with diabetes in general were overweight, cardiovascular disease did not associate with a relative excess of weight on cross-sectional study. An inverse relationship between BMI and cardiovascular disease, tentatively attributed by others to more severe diabetes or associated debility (*28,69,70*), was adequately explained in this population by lower relative BMIs associated with increasing age.

The strong association of overt albumenuria with cardiovascular disease tends to support the renal-vascular link proposed by others (*33,35*), but albumenuria was by no means a reliable marker of cardiovascular morbidity. Microalbumenuria was not significantly associated with cardiovascular disease on this cross-sectional review, however; its predictive value for future cardiovascular morbidity and mortality (*20,21,30,31*) will need evaluation by prospective study.

In view of their striking association, rigorous control of hypertension should reduce cardiovascular disease in Navajos with diabetes, probably with a more pronounced effect on stroke and peripheral vascular disease than on heart disease, as in other populations (*71*). Much progressive renal disease will thereby be averted as well. Single-dose, long-acting antihypertensive agents with neutral or salutary effects on lipid and metabolic profiles and with additive renal sparing effects (*72*) are especially promising. The prevention of heart disease probably requires more broadly based health promotion maneuvers in the whole community (*73*).

As diabetes rates rise and the current young population ages, the burden of cardiovascular disease in Navajos will probably rise further. Prospective studies are urgently needed to define its predictors and its natural history and to evaluate interventions.

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