Secular Trends in Treatment and Control of Type 2 Diabetes in an American Indian Population: a 30-Year Longitudinal Study

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Objective – Treatment guidelines for diabetes have become increasingly stringent as most research shows that more aggressive intervention reduces risks for complications. Community data on the effect of these interventions are lacking.

Research Design and Methods – Changes in the pharmacologic treatment of diabetes, blood pressure and cholesterol in adults with diabetes were analyzed in a longitudinal population-based study of American Indians from 10 independent 3-year time intervals between 1975 and 2004. Trends in drug use were assessed by logistic regression models and trends in glycemia, blood pressure and cholesterol were assessed by linear models.

Results – Among study participants the use of any medicine for treatment of diabetes increased from 53% in 1975-78 to 67% in 2002-04, \( p_{\text{trend}} < 0.0001 \). Use of insulin as a single agent declined and use of combinations of insulin and oral agents increased. In 1990-92, 23% of subjects had an HbA1c <7% and by 2002-04 the proportion had increased to 33%, \( p_{\text{trend}} < 0.0001 \). Use of antihypertensive medicine increased from 21% in 1975-77 to 58% in 2002-04, \( p_{\text{trend}} < 0.0001 \), coincident with a decline in mean systolic blood pressure from 137 mmHg in 1975-77 to 123 mmHg in 2002-04, \( p_{\text{trend}} < 0.0001 \). Lipid lowering medicine use also increased, with an accompanying increase in HDL and a decrease in non-HDL cholesterol concentration.

Conclusions – Major changes in community treatment patterns for diabetes and related conditions coincided with improvements in glycemia, blood pressure and cholesterol.

Over time there have been many revisions in the guidelines developed for care of diabetic patients (1). Large clinical trials such as the Diabetes Control and Complications Trial (DCCT) and the UK Prospective Diabetes Study (UKPDS) have shown the importance of tight glycemic control and lower blood pressure for prevention of complications in subjects with diabetes (2, 3). Furthermore, the proliferation of new anti-hyperglycemic drugs (such as metformin and the thiazolidinediones) and insulin analogues has led to greater use of combination therapy with a wider variety of agents. New and more potent medicines for blood pressure and lipid management are also now more widely available. Efforts to achieve the lower targets for blood pressure and cholesterol advocated for people with diabetes than for those without (1, 4) may be enhanced by greater use of more efficacious medicines and may lead ultimately to significant improvements in care.

The Pima Indians of central Arizona have an extraordinarily high prevalence of type 2 diabetes and have participated in a longitudinal study of health for over 40 years (5). The aim of the current study was to examine changes in medicine use over 30 years in diabetic Pima Indians who participated in this longitudinal study and to determine if changes in treatment corresponded with changes in glycemia, blood pressure, and cholesterol.

RESEARCH DESIGN AND METHODS

Individuals over 5 years old who resided in a defined area of the Gila River Indian Community were invited to participate in research examinations every 2 years, regardless of health. Primary medical care for community residents was provided separately from these research examinations, except that
clinically relevant test results (laboratory, physical examination, or other) from the research examinations, including new diagnoses of diabetes, were reported to the participants and their health care providers, and appropriate referrals were made. Diabetes was diagnosed at these research examinations by World Health Organization (WHO) criteria (6) if the plasma glucose concentration two hours after a 75g oral glucose tolerance test was \( \geq 200 \text{ mg/dl} \) or if a diagnosis was made during routine clinical care. At each examination, blood was also drawn after an overnight fast for measurement of total cholesterol, HbA1c and, since 1992, for HDL cholesterol and triglycerides. Subjects were weighed while dressed in light clothing and no shoes, and height was measured. Blood pressure was measured at the first and fourth Korotkoff sounds with the subject supine.

Plasma glucose concentration was measured using the Technicon Autoanalyzer between 1975 and October 1991 and since then by the hexokinase method. HbA1c was measured by HPLC (Biorad MDMS) from 1989 until 2000 and thereafter by HPLC (Tosoh A1c 2.2 Plus). A formula derived from duplicate analyses using both methods was used to convert the newer assay to the older assay, HbA1c \(_{\text{old method}}\) = -0.2792 + (1.0066 \times \text{HbA1c }_{\text{new method}}). Total cholesterol was measured until April 1992 by the ferric chloride/acetic acid-sulfuric acid technique (Technicon AutoAnalyzer) and thereafter by the enzymatic method, which was also used for measuring HDL cholesterol.

A questionnaire was used to record current medicine use. Prior to April 1992 medicine use was recorded in broad categories only (e.g. anti-hypertensive), but since April 1992 medicines were recorded by name and only by type when more specific information was unavailable.

The present analysis included all diabetic subjects over 18 years old who had research examinations between January 1975 and December 2004 and were not pregnant at the time of examination. Data from examinations at which diabetes was first diagnosed were not included in the analysis, since these subjects had not yet received diabetes management at these examinations. Ten independent 3-year time periods were defined. Subjects could be included in multiple time periods. When a subject had more than one examination during a time period only the examination closest to the midpoint of that time period was included. The 3-year periods were selected to minimize loss of information due to exclusion of data from repeat examinations within the same period and to be of sufficient duration that reliable prevalence estimates could be made within each period. Variables with skewed distribution (total cholesterol, HDL cholesterol, non-HDL cholesterol and triglycerides) were log transformed for analysis.

For continuous variables, relationship with time period was examined by linear regression. A numeric variable was used to represent time periods in sequential order and the resultant p-value was taken as the test for secular trend (p trend). For dichotomous variables, time trends were assessed using logistic regression. Because observations within an individual are not independent of one another, an assumption of conventional regression methods, both linear and logistic models were fit with generalized estimating equations which allow for lack of independence among observations (PROC GENMOD of SAS). Statistical significance was assessed with the “empirical” estimate of the standard error.

RESULTS

During the study, 2,019 diabetic individuals (1218 women, 801 men) attended examinations. Fifty-eight percent (n=1173) of participants attended during only 1 or 2 time periods whereas one percent (n=18) attended
examinations in ≥9 time periods. More people attended examinations in the final time period (n=775) than in earlier periods, in keeping with an increase in population size and overall clinic attendance. Table 1 shows clinical characteristics of the participants by time period. Mean age of attendees declined over the course of the study, whereas mean duration of diabetes increased. There was a trend toward higher BMIs for later time periods. The proportion of clinic attendees with diabetes was steady throughout the study period.

**Diabetes treatment.** Treatment for diabetes was categorized as oral agents only, insulin only and combined oral agents and insulin. More recently approved diabetes drugs such as exenatide or oral DPP IV inhibitors, were not used during this study period. Over the course of the study the proportion of subjects receiving medicine for diabetes increased from 53% in 1975-77 to 67% in 2002-04. Figure 1 shows changes in prevalence of the different modes of treatment. Use of combined oral agents and insulin increased from <1% in 1993-95, the first time period for which accurate data are available, to 15.9% in the final time period, \( p_{\text{trend}}<0.0001 \) adjusted for age, sex and diabetes duration. The increased use of multiple agents was accompanied by a fall in use of insulin alone from 20% in 1993-95 to 8% in 2002-04, \( p_{\text{trend}}<0.0001 \).

Data for individual drug use were available in the final 4 time periods. The prevalence of sulphonylurea use did not change, but their use as single agents declined. Use of metformin and thiazolidinediones increased, both in total use and as single agents (Table 2).

Glycemia was assessed throughout the study with fasting plasma glucose and, since 1989, with HbA1c. Figure 1a shows a downward trend for fasting glucose with a difference in mean glucose between successive time periods of -4.91 mg/dl, \( p<0.0001 \) adjusted for age, sex and diabetes duration. A similar trend occurred for HbA1c for the last 5 time periods (mean±SD 9.2%±2.4, 9.4%±2.4, 8.8%±2.5, 8.5%±2.4 and 8.2%±2.3 respectively), with a difference in mean HbA1c between successive time periods of -0.319%, \( p<0.0001 \) adjusted for age, sex and diabetes duration. A greater proportion of subjects reached the goal of an HbA1c <7.0% in the last 2 time periods than in earlier time periods and this was accompanied by a reduction in the percentage of subjects with an HbA1c ≥10%. The proportion of subjects receiving no medicine for diabetes while having an HbA1c ≥7% fell throughout the study from 26% in 1990-92 to 16% in 2002-04.

**Blood pressure.** Figure 1b illustrates the increasing use of anti-hypertensive medicines, which rose from 21% in 1975-77 to 58% in 2002-04 (\( p_{\text{trend}}<0.0001 \) adjusted for age, sex and diabetes duration). Since 1993, use of ACE inhibitors and angiotensin receptor blockers (ARBs) has increased relative to other categories of antihypertensive medicines. ACE inhibitors and ARBs were used by 22% of individuals in 1993-95 and by 48% of individuals in 2002-04. In 1993-95, diuretics, beta blockers and calcium channel blockers were used by 6%, 2% and 4% of participants respectively; whereas in 2002-04 the corresponding numbers were 16%, 7% and 12%. In 1993-95, 80% of subjects taking anti-hypertensive agents used only a single medicine, whereas by 2002-04 only 59% of subjects did so and 5% reported using 4 or more medicines for blood pressure control. Trends for use of all categories of antihypertensive medicines were positive and statistically significant, \( p<0.0001 \), after adjustment for age, sex and diabetes duration.

Mean systolic and diastolic blood pressure were highest in the first time period and declined throughout the 1970s and early 1980s. Both pressures increased again in the late 1980s, followed by a further decline in
the 1990s. Although use of antihypertensive agents increased after the initial time period, there was no reduction in use coinciding with the climb in mean systolic blood pressure in the early 1990s. The percentage of subjects who met the current ADA goal of a blood pressure <130/80 was highest in 1981-83 (52%), then decreased to a low of 34% in 1987-89, and returned to 52% in the final 2 time periods. In 1975-77, 56% of subjects had a blood pressure >130/80 and were using no antihypertensive medicines, whereas in 2002-04 the proportion of hypertensive subjects not receiving antihypertensive medicines was 18%. Overall, there was a downward trend over time for mean systolic blood pressure of 14 mmHg between 1975-77 and 2002-04 (p=0.0014) and mean diastolic blood pressure of 7 mmHg (p<0.0001), after adjustment for age, sex and diabetes duration.

*Lipids.* Data for lipid-lowering medicines are only available for the final 4 time periods. Only 1% of subjects reported use of lipid-lowering medicines in both the 1993-95 and 1996-98 time periods, the proportion increased to 14% in the final time period (p<0.0001 for trend, adjusted for age, sex and diabetes duration); 88% of drugs taken for lipid-lowering were statins. (Figure 1c)

Total cholesterol concentration varied throughout the study, with the highest geometric mean value of 185 mg/dl in 1987-89 and the lowest of 175 mg/dl in 1975-77, but the variation was not statistically significant. Likewise, the percentage of subjects meeting the ADA guidelines of a total cholesterol <200mg/dl was unchanged. However, whereas 34% of subjects had cholesterol concentrations ≥200mg/dl and were not receiving treatment in 1993-95, the proportion of those not receiving treatment declined to 23% by 2002-04 and the percentage of subjects reaching goal while on treatment increased from 0.3% to 9% over the same time period.

Since 1989, sub-fractions of cholesterol were measured, revealing a rise in HDL cholesterol and a fall in the non-HDL cholesterol fraction (Figure 3) coinciding with the increased use of cholesterol lowering agents. Serum triglyceride concentrations were unchanged over this time period.

*Goals.* Specific targets are advised for patients with diabetes concerning glycemia, blood pressure and cholesterol. Using the targets available at the close of the study, goals for treatment were HbA1c <7 %, systolic blood pressure <130 mmHg, diastolic blood pressure <80 mmHg (1) and total cholesterol <200 mg/dl (7). The proportion of patients meeting all three goals increased from 7.2% in 1990-92 to 15.7% in 2002-04 (p_{trend}<0.0001, adjusted for age, sex and diabetes duration). Female sex, younger age and shorter duration of diabetes, but not BMI, were significantly associated with reaching all goals (p<0.05) adjusted for time period.

**CONCLUSIONS**

Major changes in treatment of diabetes and related conditions have occurred in the Gila River Indian Community over the past 30 years. These changes coincide with significant improvements in glycemia, blood pressure, and serum cholesterol concentration and with a decline in the incidence of kidney failure (8). The extent to which improvements in glycemia, blood pressure and lipids have influenced incidence of diabetic complications in the community, however, cannot be determined from an observational study.

The number of new classes of drugs available to treat diabetes, blood pressure and cholesterol has increased in recent years. Drugs to lower cholesterol came into common use in the community only in the last decade, and the majority of drugs prescribed for this purpose were statins. Increased use of all major classes of blood pressure agents, including established classes, was also
observed, suggesting that increased use of medicines in recent years reflects not just use of newer drugs but an effort to meet more stringent treatment targets. In the most recent time period, 15.7% of subjects met American Diabetes Association (ADA) goals for glycemic control, blood pressure and total cholesterol; over twice the prevalence of 7.3% among diabetic persons in the NHANES survey from 1999-2003 (9). These findings are consistent with a race/ethnicity comparison of measures of diabetes control in participants at enrollment in the Look AHEAD clinical trial of adults with type 2 diabetes. Among American Indians in that study (some of whom are from this community), 12.2 % met the goals of HbA1c<7%, systolic blood pressure < 130 mmHg, diastolic blood pressure < 80 mmHg, and LDL-cholesterol < 100 mg/dl. This percentage was higher than among white, African-American, or Hispanic participants (10).

Indian Health Service (IHS) audit data show a decline in mean HbA1c from 8.9% in 1995 to 7.9% in 2001 (11), consistent with the decline in HbA1c in our study, although the mean levels at both time periods in our study were higher. The IHS also reported greater improvements in diastolic blood pressure, total cholesterol and triglycerides over this time period than in our study. However, mean values were all higher than in the present population. This finding may reflect demographic differences, as the IHS audit participants were on average older and had a shorter mean duration of diabetes than participants in our study. Moreover IHS audit data are gathered from audited medical records in which dates of diagnosis are likely not as accurate and laboratory measurements not as uniform as in our study.

Other population studies report changes in treatment patterns for glycemia (9), blood pressure (9, 10), and lipids (9) as well as outcome measures, particularly over the last decade. A shift away from single agent insulin use is reported along with increased use of hypoglycemic medicine (oral or insulin), although most studies do not report improvements in glycemic control as measured by HbA1c (9). Increases in use of antihypertensive medicines, particularly ACE inhibitors, however, are associated with reductions in mean blood pressure (9, 10). Use of lipid lowering drugs is increasing and in some studies this increase is accompanied by a fall in both total cholesterol and triglycerides (9).

While there was a trend towards lower blood pressure over time in the present study, the decline was not linear. What caused the earlier decline and rise is unclear. Increase in anti-hypertensive medicine use in the last 15 years is more marked and is associated with a fall in blood pressure from 1990-92, returning to the lower levels seen earlier in the study, when use of anti-hypertensive medicine was rarer. The increased use of anti-hypertensive medication may be a response to increased blood pressure, but may also be due to increased use of such agents to treat incipient diabetic renal disease. Our data do not permit us to distinguish between these two indications.

Despite the improvements in glycemia, blood pressure and cholesterol fractions, BMI increased throughout the study. This increase may simply reflect the increasing trend for BMI seen in the general population (9), but it could also be linked to the medicines used to treat diabetes (12) and to improvements in glycemic control (3). IHS audit data show an increase in mean BMI in diabetic American Indians between 1995 and 2004 (13) and NHANES reported an increase in obesity among diabetic subjects between 1988-94 and 1999-2000 without any overall improvement in glycemia (9).

Along with changes in available medicines and treatment goals, there have also been changes in diagnostic criteria for
diabetes which may influence our findings. In 1985 the WHO published new criteria for the diagnosis of diabetes, advocating diagnostic cut points of ≥140 mg/dl for fasting glucose and ≥200 mg/dl for 2-hour glucose (6). In 1997, the ADA proposed a move away from the oral glucose tolerance test to a reliance on fasting glucose, using the lower cut point of ≥126 mg/dl (14). The WHO also lowered the fasting cut point to ≥126 mg/dl but continues to advocate for the 2-hour glucose measurement (15). [More recent proposals to base diagnosis on HbA1c occurred after the present study (16-17).] Throughout this study we used the 2-hour glucose ≥200 mg/dl to diagnose diabetes. However, not all subjects are diagnosed in the research setting; some are diagnosed as part of routine medical care and therefore differences in diagnostic criteria may have occurred over the course of the study. When subjects were divided according to method of diagnosis, those diagnosed on the basis of a 2-hour post-load glucose of ≥200 mg/dl had lower mean fasting glucose and HbA1c than those diagnosed on clinical grounds alone.

The DCCT showed the importance of tight glycemic control for prevention of microvascular complications in subjects with type 1 diabetes (2) and the UKPDS reported similar findings in type 2 diabetes (3). However, overly intensive glycemic control in patients with long-standing type 2 diabetes may also have risks. Three recent clinical trials that sought to reduce the target hemoglobin A1c (HbA1c) to levels below <7 % (i.e., HbA1c <6-6.5 %), found no benefit on cardiovascular outcomes and one, the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial, found higher death and cardiovascular event rates with more aggressive attempts to normalize blood glucose (18-20). Each of these recent trials also reported a significantly increased risk of severe hypoglycemia in the groups with the lower HbA1c goals. As blood pressure control is important for reducing both renal and cardiovascular complications (21), lower goals for blood pressure are advocated for people with diabetes (1, 4). The benefits of lowering blood pressure and lipids, however, appear to be limited, as recently reported by the ACCORD clinical trial (22,23). Additionally, in order to reduce the high risk of cardiovascular disease in people with diabetes (24) a greater use of aspirin (1) has been encouraged. We did not report data on aspirin use in the present study, since data on aspirin use may be less accurate than data on other medicines because aspirin is non-prescription.

The changes reported in this study could represent, in part, a change in research clinic attendance pattern as opposed to a change in actual practice if, for instance, the research clinic attendees have become more likely to attend hospital clinics or have fewer complications of diabetes than non-clinic attendees. However, neither the recruitment policy for the study clinic, nor the proportion of attendees at clinic with diagnosed diabetes changed over the course of the study. The mean age of clinic attendees with diabetes as well as the mean age at onset of diabetes were younger in the more recent time periods, in keeping with a shift to an onset of diabetes at younger ages (8, 25). Medicine use is assessed by self report rather than from pharmacy records. This approach may lead to underreporting of medicines, but it may also reduce the likelihood that prescribed but untaken medicines are recorded.

In a recent 30 year period, the goals for treatment and the medicines available to meet those goals have changed considerably. The present study indicates that efforts to meet ADA treatment goals for control of glycemia, blood pressure and cholesterol have met with some success, since the prevalence of attaining these goals is over two times as high in diabetic Pima Indians in 2002-04 as in 1990-92. These improvements have been
accompanied by an increase in mean BMI. Nevertheless, improvements in the other parameters suggest that members of this community have benefitted substantially from progress in diabetes care over the last three decades.

**Author Contributions:** HCL researched data, wrote manuscript, contributed to discussion and edited manuscript; JK researched data, contributed to discussion and edited manuscript; VA researched data contributed to discussion; KK researched data and contributed to discussion; RGN researched data, contributed to discussion and edited manuscript, WCK researched data, contributed to discussion and edited manuscript; RLH researched data, contributed to discussion and edited manuscript.

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

**REFERENCES**


12. Looker HC, Knowler WC, Hanson RL. Changes in BMI and weight before and after the development of type 2 diabetes. Diabetes Care 2001;24:1917-1922


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<th>Clinical Diagnosis (%)</th>
<th>Male Sex (%)</th>
<th>Age (yrs)</th>
<th>Diabetes Duration (yrs)</th>
<th>Age at Diagnosis (yrs)</th>
<th>BMI (kg/m²)</th>
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<td>11.4</td>
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*p-trend*

- Except for the first row, all results pertain only to persons with diagnosed diabetes. Data are means with standard deviations in brackets or frequency (%). Clinical diagnosis refers to a diagnosis of diabetes made during routine clinical care rather than at a research examination (i.e., those without a clinical diagnosis had the diagnosis made at a previous research examination). P values computed for time period. For frequencies, p-values are from chi-square tests; for continuous variables p-values are computed by regression.

* *adjusted for sex; † adjusted for age and sex; ‡ adjusted for age, sex and diabetes duration.*
### Table 2. Prevalence of anti-diabetic oral agent use by type. Gila River Indian Community, 1993 - 2004

<table>
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<tr>
<th></th>
<th>1993-95 (n = 623)</th>
<th>1996-98 (n = 464)</th>
<th>1999-01 (n = 575)</th>
<th>2002-04 (n = 775)</th>
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<tr>
<td>Any use</td>
<td>254 (40.8%)</td>
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<td>213 (37.0%)</td>
<td>299 (38.6%)</td>
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<td>102 (17.7%)</td>
<td>90 (11.6%)</td>
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<td>0 (0%)</td>
<td>30 (6.5%)</td>
<td>144 (25.0%)</td>
<td>287 (37.0%)</td>
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<td>1 (0.2%)</td>
<td>23 (4.0%)</td>
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<tr>
<td>Any use</td>
<td>0 (0%)</td>
<td>5 (1.1%)</td>
<td>46 (8.0%)</td>
<td>154 (19.9%)</td>
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<tr>
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<td>0 (0%)</td>
<td>1 (0.2%)</td>
<td>2 (0.3%)</td>
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Data are number with percentages of all subjects in each time period in brackets. “Any use” indicates all subjects reporting use of the drug and “Alone” indicates subjects who are taking the drug as their only therapy for diabetes. OR are the odds ratios per time period adjusted for age, sex and diabetes duration. P-value for trend adjusted for age, sex and diabetes duration.
**Figure Legends**

**Figure 1: Trends in treatment over time**

**A** – *Diabetes treatment by category over time and mean fasting glucose over time*; For time periods prior to 1993 combined use of oral agents and insulin was not recorded separately but included as insulin use. After 1993 data were available to show combined insulin and oral agent use – this is shown as a hatched area of the insulin use column.

Trend for oral agent only use $p<0.0001$; Trend for insulin only use $p<0.0001$; Trend for combined oral agents and insulin use $p<0.0001$; Trend for mean fasting glucose, change = -4.9 mg/dl per 3-year time period, $p<0.0001$. All trends adjusted for age, sex and diabetes duration.

**B** – *Antihypertensive use and mean systolic and diastolic blood pressure over time*; Trend for antihypertensive agent use, $p<0.0001$; Trend for mean systolic blood pressure parameter estimate = -0.37 mmHg per 3-year time period, $p=0.0014$; Trend for mean diastolic blood pressure parameter estimate = -0.37 mmHg, $p<0.0001$. All trends adjusted for age, sex and diabetes duration.

**C** – *Lipid lowering medicine use and geometric mean total, HDL, non-HDL cholesterol and triglycerides over time*; Trend for lipid lowering agent use $p<0.0001$; Trend for total cholesterol, change = 0.0004 mg/dl, $p=0.77$; Trend for HDL cholesterol, change =0.051 mg/dl, per 3-year time period $<0.0001$; Trend for non-HDL cholesterol, change = -0.046 mg/dl, $p<0.0001$; Trend for triglycerides, change = -0.015 mg/dl, $p=0.16$. All trends adjusted for age, sex and diabetes duration.

**Figure 1a**