INTRODUCTION

The Census 2000 has reported Latinos as the fastest growing ethnic group in the US, and Mexican Americans as leading growth among Latinos (1, 2). Many older Mexican Americans suffer from a variety of chronic illnesses, and diabetes appears to be one of the major clinical and public health challenges among them (3–6). Five large-scale epidemiological studies focusing on Hispanic Americans have established that the prevalence of diabetes is two to three times greater in Mexican Americans than in their non-Hispanic white counterparts (7–11).

Impact of Antidiabetic Medications on Physical and Cognitive Functioning of Older Mexican Americans with Diabetes Mellitus: A Population-based Cohort Study

JASMANDA H. WU, PhD, MARY N. HAAN, DrPH, JERSEY LIANG, PhD,
DEBASHIS GHOSH, PhD, HECTOR M. GONZALEZ, PhD,
AND WILLIAM H. HERMAN, MD

PURPOSE: The current study was designed to evaluate the utility of antidiabetic medications in affecting changes in physical and cognitive functioning among older Mexican Americans with diabetes over a 2-year period.

METHODS: A longitudinal analysis with repeated measurements between 1999 and 2001 was performed in a cohort of Mexican Americans, 60 or older, in the SALSA Project. Statistical analysis was conducted using a generalized estimating equation.

RESULTS: For subjects with diagnosed diabetes ≤ 5 years (N = 381), there was less decline in physical and cognitive functioning over 2 years among subjects on treatment, compared to those without treatment. For subjects with diagnosed diabetes of 5+ years (N = 337), the effect of antidiabetic medications was more significant in preventing the decline in physical and cognitive functioning (ADL: mean in log scale = −0.10, 95% CI = −0.16, −0.04, 3MS: mean = 6.35, 95% CI = 3.23, 9.48). Combination therapy of antidiabetic agents appeared to be more effective than monotherapy in preventing the decline in physical and cognitive functioning for subjects.

CONCLUSIONS: Antidiabetic drugs appear to be useful in alleviating the decline in physical and cognitive functioning among older Mexican Americans with diabetes, especially for those with a longer duration of the disease.

Ann Epidemiol 2003;13:369–376. © 2003 Elsevier Inc. All rights reserved.

KEY WORDS: Diabetes mellitus, Mexican Americans, Antidiabetic drugs, Physical and cognitive functioning.

Diabetes is a chronic illness, which requires ongoing medical care to prevent acute symptoms and reduce the risk of long-term complications (12–14). The onset and progression of long-term complications in diabetic patients are caused by hyperglycemia (15). The American Diabetes Association (ADA) has recommended that blood glucose levels be maintained at or near normal. Ample data demonstrate that normalizing blood glucose level in diabetic subjects reduces retinopathy, nephropathy, and neuropathy (16–19).

In addition to efficacy of medical treatment in clinical outcomes, there is growing interest in the impact of medical treatment on patient health status and health-related quality of life (HRQOL), which could assist physicians in making decisions about alternative drug therapies and regulatory approval process (20). There are studies which demonstrated the short-term benefits of improved glycemic control in improving cognitive decline and functional restrictions in daily activities in diabetic patients (21–24). In a controlled clinical trial, Gradman found that after two months of treatment with glipizide, patients were able to recall significantly more words than before treatment (p = 0.005). Although patients in the control group showed some im-
The vast majority of studies examining the efficacy and patient health status of antidiabetic drugs were clinical trials (21–24). However, clinical trials usually focus on selected subsets of patients with strict inclusion and exclusion criteria and close monitoring. Consequently, whether these agents are effective in controlling physical and cognitive functioning in a naturalistic environment, especially among the less studied ethnic groups, such as the Mexican Americans, is not known. As a result, our understanding of the relationship between antidiabetic drug treatment, glycemic control, and physical and cognitive functioning among Mexican Americans is very limited.

Older Mexican Americans generally have a higher prevalence of diabetes, its complications, other comorbidities, lower education level and social economic status, compared with non-Hispanic whites (25–28). In addition, some studies suggested that Mexican Americans with diabetes infrequently self-monitored their blood glucose, and failed to have regular clinical follow-up (29–30). Poor diabetes management among older Mexican Americans is often associated with increase in morbidity and mortality.

Our previous research suggested that older Mexican Americans with diabetes had a higher rate of decline in physical and cognitive functioning than their non-diabetic counterparts (31–32). Decline in physical and cognitive functioning often leads to disability and dementia (33–36). Disability is often associated with an increase in hospitalization, institutionalization, and loss of economic self-sufficiency (37–38). The impact of dementia on society and its associated direct and indirect costs are enormous. The related social and economic burden of dementia is approaching $100 billion annually in the United States (39–41). Knowledge of the effectiveness of antidiabetic drugs on attenuating the decline in physical and cognitive functioning may help to reduce the social and economic burden of diabetes.

In this study, we examine the utility of antidiabetic medications in improving health-related quality of life among a population-based sample of older Mexican Americans. We focus on two domains: physical and cognitive functioning. We hypothesize that there is a significant difference in the 2-year change of physical functioning, global cognitive function, and verbal learning memory among older diabetic Mexican Americans under active antidiabetic drug treatment, compared with those without treatment.

### METHODS

#### Study Population

Study population was the participants diagnosed as having diabetes at baseline or follow-up years in the Sacramento Area Latino Study on Aging (SALSA) project. SALSA participants were recruited from the Sacramento Metropolitan area and four surrounding rural counties in California in 1998–1999. The eligible criteria were age 60 or older in 1998 and self-designated Latino. A detailed description of the sampling frame and recruitment in SALSA is in a separate report (42).

#### Data Collection

Baseline data collection began in 1998 and was completed in 1999. The first and second follow up visits were completed in 2000 and 2001, respectively. The SALSA participants were interviewed in the language of choice at the participants' homes. In the treatment group, 6% of the participants were deceased, 2% were lost to follow up, and 12% refused further follow up at the end of the second year. In the non-treatment group, 5% of the participants were deceased, 4% were lost to follow up, and 10% refused further follow up at the end of the second year. This study analyzed data from baseline through second follow up.

#### Analysis Approach

A total of 718 diabetic subjects in SALSA were divided into two groups (based on the duration of diabetes) to examine the effect of antidiabetic medications. This approach, based on different duration of diabetes, would offer a better assessment of the actual management scenario for these patients as the initial treatment for early stage diabetic patients generally involves only diet and exercise. It is not until diet and exercise fail to control the diabetic conditions would these patients turn to antidiabetic medication treatments.

#### Measurement

**Diabetes** Diabetes was ascertained using a combination of medical history, drug use, and fasting plasma glucose. Participants who met any of the following criteria at baseline or follow-up were characterized as having diabetes: 1) Fasting plasma glucose (FPG) level ≥ 126mg/dl (7.0 mmol/l) (fasting was defined as no caloric intake for at least 8 h); or 2) Use of an antidiabetic medication; or 3) Self-report of a doctor's diagnosis of diabetes.

**Antidiabetic Drugs** Use of diabetic medications was ascertained by direct inspection of medications at participants' homes at baseline and at each annual visit. Antidiabetic
Drugs include insulin and oral glucose-lowering agents. The oral glucose-lowering agents include: sulfonylureas (e.g., chlorpropamide, tolazamide, glimepiride, glipizide, and glyburide), biguanide (e.g., metformin), thiazolidinediones (glitazones) (e.g., pioglitazone, rosiglitazone, and troglitazone), α-glucosidase inhibitors (e.g., acarbose and meglitinide), and meglitinides (e.g., repaglinide).

**Physical and Cognitive Functioning** This study focused on self-reported physical functioning in personal care (basic activities of daily living, ADL) and household management (instrumental activities of daily living, IADL) (43–44). ADL is comprised of 7 items to measure the ability to walk, eat, toilet, transfer, dress and bathe. IADL is comprised of 15 items to measure the ability for household management such as the ability to prepare own meals, and do housework, etc. The respondent is asked to rate his or her ability to perform these activities on a 4-point scale that ranges from “I have no difficulty” to “I can only do it with assistance”. These are standardized scales widely used in epidemiologic research in elderly populations. Cognitive functioning was measured by the Modified Mini Mental State Exam (3MS) and a Delayed Word List recall of the Spanish-English verbal learning test (45–47). MMSE is a brief, general test with concentration, language, and memory components used to screen subjects for dementia. The delayed word list recall test utilizes 15 words that are presented in five sequential learning trials, followed by a distracter list, and then by delayed recall of the original list (47).

**Other Variables** Duration of diabetes was assessed by self-report at baseline. Diabetic symptoms were assessed by self-report of: lack of strength (energy), sleepiness or drowsiness, difficulty concentrating, thirst, urination, etc. (21). Complication-related symptoms were also assessed by self-report of: numbness (loss of sensation) in the feet, numbness (loss of sensation) in the hands, and sudden deterioration of vision, etc. (21).

Diagnosis of hypertension was ascertained using a combination of medical history and measured blood pressure. Participants who met either of the following criteria were characterized as having hypertension: 1) Systolic pressure of 140 mmHg or higher and/or a diastolic pressure of 90 mmHg or higher; or 2) Self-report of a doctor’s diagnosis of hypertension or high blood pressure.

Stroke, heart attack, nephropathy, and diabetic retinopathy were assessed by self-report of a doctor’s diagnosis. Amputation was assessed by direct observation. Depression was measured with the CES-D scale (48). Education, medical insurance, household income, smoking status, alcohol use and physical activity were assessed in the home visit.

**Statistical Methods**

Statistical analysis was performed using PC-SAS (ver. 8.1). Descriptive analysis was performed using Chi-square or linear regression. The impact of antidiabetic medications on change in physical and cognitive functioning was conducted using a longitudinal analysis based on measurements at three time points. A generalized estimating equation (GEE) was used (e.g., using proc genmod in SAS). A 0.05 level of significance was used for all the analysis.

A summary score was created as a continuous variable for each of ADL, IADL, 3MS and word-list test. Each summary score for ADL and IADL was log-transformed to achieve normality. Use of antidiabetic drugs was coded as a dichotomous independent variable (0 and 1). The effect of antidiabetic treatments on 2-year change in physical and cognitive functioning for each subject was specified by including the variable time from baseline through the second follow-up in the model. An interaction term between antidiabetic drugs and time was used to test the hypotheses that physical or cognitive functioning change over 2 years was less among those using antidiabetic drugs (a simple linear model was assumed).

GEE requires missing data completely at random. Thus, to evaluate the missing data mechanism, the participants were stratified into three groups, and the outcome variables at the baseline were compared among these three groups. The results suggested that the missing probability depends on outcome variables, and the missing data mechanism was not completely at random (respondents vs. non-respondents vs. death: ADL = 0.80 vs. 0.90 vs. 3.05; IADL = 6.81 vs. 8.60 vs. 12.25; 3MS = 84.19 vs. 80.92 vs. 73.80; and word-list test = 8.15 vs. 8.05 vs. 6.59).

Thus, multiple imputation (e.g., using proc mi and proc mi-analyze in SAS) was used to impute missing data in conjunction with the GEE method (49–51). The imputation model, which included the demographic variables, socio-economic status, medical history, diabetic medications and outcome of interests, was essentially the same as the analysis model. The baseline values (e.g., ADL, IADL, 3MS, word-list test) were a good estimate of follow-up values and were used for imputation. Any missing data for the total score of ADL, IADL, 3MS, and word-list test as well as associated covariates were imputed. A total of five imputed data sets was used in the analysis.

Confounding factors were evaluated, depending on their influence on the main effect terms or from the literature. For instance, age was considered a confounder, as the coefficient estimate of antidiabetic medications increased more than 10% in the presence of age variable.

**RESULTS**

Among the 1789 study participants in the SALSA Project, 585 (32.7%) were identified as having diabetes at baseline. Among those with diabetes, 56% were women and 44% were men. There were 341 diabetic subjects (58.3%) who used either oral antidiabetic medications or insulin. Sulfonylureas
were the most common class of diabetic drugs, and 74% of the diabetic drug users (253 subjects) used either a sulfonylurea or a combination of a sulfonylurea with another antidiabetic medication (Table 1).

A total of 718 diabetic subjects, including 585 diagnosed at baseline and 133 from follow-up years, were divided into two groups based on the duration of diagnosed diabetes to examine the utility of antidiabetic medications.

### Duration of Diagnosed Diabetes \(\leq 5\) Years

Table 2 compares the baseline characteristics of diabetic subjects by treatment status and duration of diabetes. Among those with disease duration \(\leq 5\) years, age, gender and education levels were similar between the treated and untreated groups. The treated group had a higher percentage of reported medical insurance and longer duration of diabetes than the untreated group.

At baseline, in those with \(\leq 5\) years duration, the treatment group reported more diabetes and complication-related symptoms, but the differences were not significant. The treatment group also reported more hypertension, stroke, MI, diabetic retinopathy, and kidney problems, but the differences were not statistically significant. The fasting plasma glucose level was also higher in the treatment group.

Overall, the treatment group appeared to have more severe disease than the non-treatment group.

There was no significant difference in baseline functional limitations and cognitive scores between the two groups, when

### TABLE 1. Use of antidiabetic medications at baseline

<table>
<thead>
<tr>
<th>Class of antidiabetic drugs</th>
<th>Number of subjects</th>
<th>% among diabetic subjects (N = 585)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylurea</td>
<td>253</td>
<td>43.2%</td>
</tr>
<tr>
<td>Chlorpropamide</td>
<td>1</td>
<td>0.2%</td>
</tr>
<tr>
<td>Tolazamide</td>
<td>49</td>
<td>8.4%</td>
</tr>
<tr>
<td>Glimepiride</td>
<td>5</td>
<td>0.9%</td>
</tr>
<tr>
<td>Glipizide</td>
<td>76</td>
<td>13.0%</td>
</tr>
<tr>
<td>Glyburide</td>
<td>122</td>
<td>20.9%</td>
</tr>
<tr>
<td>Biguanide – Metformin</td>
<td>118</td>
<td>20.2%</td>
</tr>
<tr>
<td>Thiazolidinediones – Trolitazone</td>
<td>16</td>
<td>2.7%</td>
</tr>
<tr>
<td>Alpha-glucosidase inhibitors – Acarbose</td>
<td>3</td>
<td>0.5%</td>
</tr>
<tr>
<td>Insulin</td>
<td>144</td>
<td>24.6%</td>
</tr>
<tr>
<td><strong>Totals on treatment of any kind</strong></td>
<td>341</td>
<td>58.3%</td>
</tr>
</tbody>
</table>

### TABLE 2. Baseline characteristics of diabetic subjects by duration and treatment status

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Diabetes (\leq 5) years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treated (N = 381)</td>
</tr>
<tr>
<td></td>
<td>Treated (N = 337)</td>
</tr>
<tr>
<td>Age (mean, SE)</td>
<td>70.6 (0.7)</td>
</tr>
<tr>
<td>Sex (% female)</td>
<td>51.3</td>
</tr>
<tr>
<td>Education (years)</td>
<td>7.15 (0.53)</td>
</tr>
<tr>
<td>Medical insurance (% with)*</td>
<td>95.6</td>
</tr>
<tr>
<td>Disease duration (y) (range)</td>
<td>3.07 (0.16)</td>
</tr>
<tr>
<td>Depressive symptoms (mean, SE)</td>
<td>10.15 (1.03)</td>
</tr>
<tr>
<td>Diabetic symptoms (mean, SE)</td>
<td>4.13 (0.37)</td>
</tr>
<tr>
<td>Symptoms related to complications (mean, SE)</td>
<td>3.03 (0.36)</td>
</tr>
<tr>
<td>Hypertension (% with)**</td>
<td>78.2</td>
</tr>
<tr>
<td>Stroke (% with)</td>
<td>13.3</td>
</tr>
<tr>
<td>Myocardial infarction (% with)</td>
<td>12.4</td>
</tr>
<tr>
<td>Diabetic retinopathy (% with)</td>
<td>2.8</td>
</tr>
<tr>
<td>Kidney disease (% with)</td>
<td>11.8</td>
</tr>
<tr>
<td>Amputation (% with)</td>
<td>0</td>
</tr>
<tr>
<td>Fasting plasma glucose (mean, SE)*</td>
<td>156.3 (4.8)</td>
</tr>
<tr>
<td>Systolic blood pressure (mean, SE)</td>
<td>141.4 (1.8)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mean, SE)</td>
<td>75.5 (1.0)</td>
</tr>
<tr>
<td>Activities of daily living</td>
<td>0.98 (0.24)</td>
</tr>
<tr>
<td>Instrumental activities of daily living</td>
<td>5.79 (0.55)</td>
</tr>
<tr>
<td>Modified Mini-mental State Exam</td>
<td>85.7 (0.9)</td>
</tr>
<tr>
<td>Delayed word list recall</td>
<td>8.68 (0.24)</td>
</tr>
</tbody>
</table>

Within \(\leq 5\) years duration group:
* \(p < 0.007\)
* \(p < 0.0001\)
** \(p = 0.05\)

Within \(> 5\) years duration group:
* *education: \(p = 0.003\)
** Mi: \(p = 0.009\)
controlling for complication-related symptoms and other confounders among those with duration ≤ 5 years.

Table 3 shows the multivariate regression analysis for the change in physical and cognitive functioning over a 2-year follow-up. The column labeled “estimate” indicates the average change in cognitive score or functional score over the 2-year time period. The term “Diabetic Tx*Year” indicates that those who were not treated declined > 2 points in 3MS score over 2 years, more than those who were treated. The functional status in untreated diabetics worsened more rapidly over time, about 0.06 points over 2 years. Overall, there was less decline in physical and cognitive functioning over 2 years among diabetic subjects who were treated with antidiabetic drugs, when controlling for age, complication-related symptoms and stroke.

**Duration of Diagnosed Diabetes of 5+ Years**

Table 2 compares the baseline characteristics of diabetic subjects with duration of diabetes of 5+ years (N = 337) who were receiving antidiabetic drugs and those not receiving antidiabetic medications. The age, gender and average duration of diabetes were similar between the two groups. The treated group had lower education level (p = 0.003).

At baseline, there was no significant difference in terms of diabetes and complication-related symptoms between the treatment and no-treatment group. There was also no significant difference between the two groups in reported hypertension, stroke, MI, diabetic retinopathy, kidney problems, and amputation.

Although there was no significant difference in baseline functional limitations and cognitive score between the groups, the treatment group reported less ADL and IADL limitations and had higher cognitive score, when controlling for other confounders.

Table 4 shows the results of the multivariate regression analysis for the change in physical functioning and cognitive score over a 2-year follow-up. The 3MS scores in the untreated group declined by more than 6 points faster in 2 years (6.4) compared with the treated group. There was less decline in functional status over a 2-year period among diabetic subjects who were treated with antidiabetic drugs, when controlling for age and education level (ADL: mean in log scale = −0.10, 95% CI = −0.16, −0.04).

Overall, when comparing with the results from the earlier group of patients with diabetes duration ≤ 5 years, the magnitude of the effect of antidiabetic drugs on physical functioning and cognitive score was larger in the group of patients with diabetes of 5+ years duration. For example, in the ≤ 5 years group, change on the 3MS was 2 points over 2 years, whereas in the > 5 years group change was > 6.

**Benefits of Monotherapy vs. Combination Therapy of Antidiabetic Drugs**

A combination therapy of two or more antidiabetic agents was found to be more effective than monotherapy alone in controlling decline in physical and cognitive functioning among patients with diabetes of 5+ years (Figure 1). For in-
stance, there was a 6.5 point increase in the 3MS score among diabetic subjects using combination therapy compared with a 4.9 point increase among those on monotherapy, when no treatment was used as the reference group (3MS: combination use = 6.51, 95% CI = 3.07, 9.94; monotherapy = 4.94, 95% CI = 2.02, 7.87). Monotherapy includes use of a sulfonylurea, metformin or thiazolidinedione, while combination therapy includes the combination therapy of a sulfonylurea, metformin or thiazolidinedione with insulin or metformin with insulin.

### DISCUSSION

The current study is the first longitudinal analysis with repeated measurements to evaluate the utility of antidiabetic drugs on attenuating decline in physical and cognitive functioning in a naturalistic environment among older Mexican Americans with diabetes. Our results demonstrate that older diabetic Mexican Americans on antidiabetic drugs had reported less ADL limitations and had less decline in their 3MS score than those not on antidiabetic drugs. This observation was more apparent in those with a longer duration of the disease.

Our results are consistent with other studies of physical and cognitive functioning (21–24). Testa et al. found better cognitive functioning and visual analog scale (VAS) assessed QOL among diabetic patients on active therapy with glipizide. In addition, patients in the active treatment group also had greater productive capacity and fewer bed-days and restricted-activity days (21).

Combination therapy was found more effective than monotherapy alone in controlling decline in physical and cognitive functioning. Our results are consistent with the findings from clinical trials using fasting serum glucose and HbA1c as outcome measures (52–55). One possible explanation for this observation is that different antidiabetic drugs might have different mode of action and safety profile. Thus, combination therapy of appropriate doses of different agents might potentially maximize the synergy between agents in terms of safety and efficacy. This, in turn, might enhance patients’ compliance, thus exploiting the full benefits of pharmacological interventions (52–57).

The decline in physical and cognitive functioning often leads to disability and dementia. Disability and dementia are both important social, economic, and public health issues and are often associated with impaired quality of life with substantial direct and indirect health care costs. Our results indicated that antidiabetic drugs appear to be useful in reducing decline in physical and cognitive functioning among older Mexican Americans with diabetes, especially for those with a longer duration of the disease. The findings of this research might provide some useful implications to the Mexican American community to encourage adequate use of antidiabetic medications to reduce the potential social and economic burden among its members. In addition, physical and cognitive functioning improvement could perhaps be considered as one of the long-term outcomes to gauge the effectiveness of antidiabetic agents for clinicians who take care of older diabetic patients.

The strengths of this study include the fact that the study participants were followed in a naturalistic environment, which could reflect the actual situation related to diabetes management. In addition, a population-based sample of older individuals was included in the study.
There are several directions that future researchers in this field could consider: First, the effectiveness of individual antidiabetic agent on physical and cognitive functioning could be further evaluated, as different agents in the same class may perform differently. Second, conducting cost-effectiveness/cost-utility analysis of different antidiabetic agents may assist physicians and patients in making decisions about alternative drug therapies. Third, incorporation of HbA1c measurement to reflect overall glycemic control of the study subjects might be helpful in analyzing the role of hyperglycemia. Fourth, other classes of medications, such as ACE inhibitors and β-blockers, may play an important role in modulating the effect of antidiabetics and their influence could be examined. Last, to confirm our findings, future research focusing on a long-term impact or in a different ethnic population or study setting may be warranted.

This study was funded by the National Institute on Aging (NIA# 12975).

REFERENCES


