Type 2 Diabetes and 10-Year Risk of Dementia and Cognitive Impairment Among Older Mexican Americans

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OBJECTIVE—Type 2 diabetes has been linked with increased risk of dementia and cognitive impairment among older adults and with premature mortality in young and middle-aged adults. No studies have evaluated the association between diabetes and dementia among Mexican Americans, a population with a high burden of diabetes. We evaluated the association of diabetes with incidence of dementia and cognitive impairment without dementia (CIND) among older Mexican Americans while accounting for competing risk from death.

RESEARCH DESIGN AND METHODS—This study included 1,617 participants 60–98 years of age from the Sacramento Area Latino Study on Aging followed up to 10 years from 1998. We evaluated the association between diabetes and dementia/CIND with competing risk regression models.

RESULTS—Participants free of dementia/CIND at baseline (n = 1,617) were followed annually up to 10 years. There were 677 (41.9%) participants with diabetes, 159 (9.8%) incident dementia/CIND cases, and 361 (22.3%) deaths. Treated and untreated diabetes (hazard ratio 2.12 [95% CI 1.65–2.73] and 2.15 [1.58–2.93]) and diabetes/CIND (2.48 [1.75–3.51]) were associated with an increased risk of death. In models adjusted for competing risk of death, those with treated and untreated diabetes had an increased risk of dementia/CIND (2.05 [1.41–2.97] and 1.35 [0.93–2.98]) compared with those without diabetes.

CONCLUSIONS—These findings provide evidence that the association between type 2 diabetes and dementia/CIND among Mexican Americans remains strong after accounting for competing risk of mortality. Treatments that modify risk of death among those with diabetes may change future dementia risk.

Type 2 diabetes is a common and established risk factor for vascular disease and mortality (1). Prevalence of type 2 diabetes is higher among older adults, and several minority racial/ethnic groups in the U.S. are disproportionately affected. Several prospective epidemiologic studies have found that older adults with type 2 diabetes have an approximately twofold increased risk of dementia (2–9), but others have not (10–13), and the mechanism is controversial (14,15). Possible mechanisms linking type 2 diabetes to dementia and cognitive impairment include chronic hyperglycemia or hypoglycemia, hyperinsulinemia or insulin resistance, effects of inflammatory cytokines and oxidative stress, and β-amyloid deposition in the brain (14,15). The type 2 diabetes–dementia association has not been evaluated among Mexican Americans, a population with a high prevalence of type 2 diabetes (16), poor glycemic control among those with diabetes (17), and higher rates of complications compared with non-Hispanic whites (18).

Mortality occurs at younger ages among people with type 2 diabetes (19). Mortality rates are nearly twice as high among people with type 2 diabetes compared with people without diabetes (19–21). Cognitive decline is also associated with higher mortality rates (22,23). Premature death in those with diabetes may influence the risk of dementia or cognitive impairment associated with type 2 diabetes. Previous studies of the association between type 2 diabetes and dementia have not accounted for competing risk of death. In this paper, we evaluate the association between type 2 diabetes and incidence of dementia and cognitive impairment without dementia (CIND) in a cohort of older Mexican Americans followed for 10 years, accounting for the competing risk of death.

RESEARCH DESIGN AND METHODS

Study population Participants included in this analysis were from the Sacramento Area Latino Study on Aging (SALSA), a cohort study of community-dwelling older Mexican Americans in the Sacramento area of California designed to evaluate the effects of metabolic and cardiovascular risk factors on dementia in this understudied ethnic group. Recruits were eligible to participate in this study if they were 60 years of age or older at enrollment in 1998–1999, resided in a six-county area in the Sacramento Valley (Sacramento, Yolo, Sutter, Solano, San Joaquin, and Placer counties), and self-identified as Latino. A detailed description of study sampling and procedures has been published elsewhere (24). A total of 1,789 participants enrolled between 1998 and 1999 were interviewed in their homes every 12–15 months for up to seven study visits ending in 2007. Every 6 months between home visits, a 10-min phone call was made to update contact information, health status, and medication changes. All participants provided written informed consent. SALSA has been approved annually by the institutional review board of the University of California, San Francisco.

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review boards of the University of California at San Francisco and Davis and the University of Michigan.

**Diabetes**

At each study visit, diabetes classification was based on fasting glucose level ≥126 mg/dL, antidiabetic medication use, or self-reports of a physician diagnosis at any study visit prior to dementia/CIND, death, or last study visit. Diabetic medications were recorded at every study visit by direct visual inspection of medications and classified using the Centers for Disease Control and Prevention Ambulatory Care Drug Database (http://www2.cdc.gov/drugs/). Given the advanced age of the cohort, most, if not all, cases were probably type 2 diabetes (16). Hereafter, we will use the term diabetes to refer to type 2 diabetes.

**Dementia and CIND**

The classifications of dementia and CIND were determined at all home visits by a multistage assessment protocol, which has been described extensively elsewhere (24). In brief, at each visit, two cognitive screening tests were used to determine the need for further neuropsychological evaluation: the Modified Mini-Mental State Exam (3MSE) (25), a global cognitive function test, and a delayed word recall trial from the Spanish English Verbal Learning Test (SEVLT) (26), a word list-learning and memory test. At baseline, a participant was referred for further evaluation if his or her score on either test fell below the 20th percentile. At follow-up, a participant was referred for a neuropsychological test battery and a standard neuropsychological examination by a geriatrician if his or her follow-up score declined from the baseline score by more than eight points on 3MSE or more than three points on SEVLT and the score fell below the 20th percentile. A team of neuropsychologists and a neuropsychologist reviewed all potential dementia and CIND cases and classified participants as demented, CIND, or cognitively normal. Standard diagnostic criteria were applied for dementia (DSM-IV) (27), Alzheimer disease (National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer’s Disease and Related Disorders Association) (28), and vascular dementia (California Alzheimer’s Disease Diagnostic and Treatment Centers) (29). Dementia and CIND cases were referred for magnetic resonance imaging. For participants who died during the study period without a previous diagnosis of dementia or CIND, dementia diagnoses were also ascertained from death certificates based on the following causes of death listed anywhere on the death certificate: dementia in Alzheimer disease, vascular dementia, other dementia, or unspecified dementia. For this analysis, dementia and CIND were combined into one outcome, dementia/CIND.

**Mortality**

Mortality ascertainment included interviews with family members to track participants who could not be reached for annual study visits or interim 6-month phone calls, online surveillance of death notices, and review of the Social Security Death Index, the National Death Index, and vital statistics data files from the state of California. Mortality surveillance is ongoing, but this analysis is limited to deaths that occurred during active follow-up for dementia/CIND (1998–2007). We had complete or partial social security numbers on most (80%) of the deceased and obtained death certificates and cause of death for 93.1% of deceased participants. We classified cause of death using ICD-10.

**Other variables**

At the baseline interview, participants reported their age, sex, years of education, country of birth, whether or not they had a regular medical doctor (as a marker of access to medical care), smoking status, and any alcohol use. As a marker of physical activity, participants were asked to classify their usual outdoor walking pace as never walks outdoors/unable to walk, easy pace, or brisk pace. Depressive symptoms were measured by the Center for Epidemiologic Studies Depression Scale, a widely used scale (range 0–60) (30). Fasting blood samples were taken at annual study visits. Fasting glucose was measured with the Cobas Mira Chemistry Analyzer (Roche Diagnostics Corporation, Indianapolis, IN). Fasting insulin was measured using a double-antibody radioimmunoassay using 125I-labeled human insulin tracer (Linco Research, St. Charles, MO), a guinea pig antiporcine insulin first antibody (Michigan Diabetes Research and Training Center, Ann Arbor, MI), and a goat anti-guinea pig γ-globulin (Antibodies Incorporated, Davis, CA) and standardized against the Human Insulin International Reference Preparation for Insulin. Sitting systolic and diastolic blood pressure measurements were taken with an automatic digital blood pressure monitor twice at a 10-min interval and averaged. Hypertension was based on measured systolic blood pressure (≥140 mmHg), self-report of a physician diagnosis, and/or antihypertensive medication use. Waist circumference was measured at the level of the umbilicus at midrespiration with the participant standing erect. History of stroke was based on self-report of a physician diagnosis and hospitalization.

**Statistical analysis**

The objective of the analysis was to examine the association of diabetes with incidence of dementia/CIND and to account for the competing risk of mortality. We first compared baseline descriptive characteristics by treated and untreated diabetes status (ever vs. never during study) with ANOVA for continuous variables and χ² tests for categorical variables.

We evaluated the association of treated and untreated diabetes with incidence of dementia/CIND using competing risk regression models with the method proposed by Fine and Gray (31). Participants were observed from study entry until the occurrence of dementia/CIND (the event of interest), death (the competing event), or censoring (last date of contact). We used time-dependent diabetes as the exposure variable for all models to capture all diabetes cases that occurred prior to diagnosis of dementia, death, or censoring (last date of contact). We used time-dependent diabetes as the exposure variable for all models to capture all diabetes cases that occurred prior to diagnosis of dementia, death, or censoring (last date of contact). We used time-dependent diabetes as the exposure variable for all models to capture all diabetes cases that occurred prior to diagnosis of dementia, death, or censoring (last date of contact). We used time-dependent diabetes as the exposure variable for all models to capture all diabetes cases that occurred prior to diagnosis of dementia, death, or censoring (last date of contact).
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We examined the influence of covariates on the association of diabetes (time dependent) with risk of dementia/CIND with a series of models. We evaluated whether dementia/CIND incidence differed among those with diabetes who were taking antidiabetic medications from those with diabetes who were not taking antidiabetic medications using a three-level exposure variable (no diabetes, untreated diabetes, and treated diabetes). Model 1 was adjusted for age (as timescale), sex, and years of education. Model 2 further adjusted for waist circumference (time dependent) to control for central obesity as a potential confounder. Model 3 (fully adjusted model) added adjustment for (time dependent) stroke to model 2 to account for stroke as a potential intermediary variable between diabetes and dementia/CIND. We assessed whether stroke modified the effect of diabetes on dementia/CIND risk by adding a multiplicative interaction term between stroke and diabetes to model 3. In analyses not reported here, we adjusted for hypertension, depressive symptoms, alcohol use, smoking status, outdoor walking pace, and having a regular medical doctor as potential confounders but did not include these variables in the final models because they did not substantially (i.e., ≥10%) alter the magnitude of the HRs for diabetes. We graphically displayed the estimated cumulative incidence of dementia/CIND by diabetes status from the fully adjusted competing risk regression model (Fig. 2).

We separately evaluated the association between dementia/CIND or diabetes and death with Cox regression models adjusted for the same covariates included in the models of the association of diabetes with risk of dementia/CIND described above. Summary statistics were run using SAS 9.2 (SAS Institute Inc., Cary, NC). All regression models were run in Stata 11 (StataCorp, College Station, TX). Competing risk regression models were estimated using Stata command stcrreg, and cumulative incidence curves were estimated using Stata command stcurve with option cif.

**RESULTS**—Figure 1 shows the flow of study participants throughout the study. A total of 1,789 adults ≥60 years of age were enrolled in SALSA in 1998–1999. A total of 172 participants were excluded from this analysis: 115 had dementia/CIND at the baseline visit and 57 did not participate in any follow-up visits. The resulting sample size was 1,617 participants at risk for dementia/CIND. Out of the 1,617 participants, 677 (41.9%) had diabetes during the study \( n = 513 \) baseline diabetes cases; \( n = 164 \) incident diabetes cases). The majority (77%) of participants with diabetes were using antidiabetic medications. There were 159 incident dementia/CIND cases. A total of 24 (15.1%) of the dementia/CIND cases were ascertained only from death certificates. Of those, 83.3\% (\( n = 20 \)) had a cognitive test score below the cut point for dementia assessment. A total of 298 participants died during the study period without a diagnosis of dementia/CIND. The remaining 1,160 participants were censored at the age of last contact with the study. In addition to the deaths that occurred among participants without dementia/CIND, 63 participants with dementia/CIND died during the study period, for a total of 361 deaths. Average nonmortality annual attrition due to refusals and loss to follow-up was 2.9% per year. The mean follow-up time was 6.5 years (SD 2.5 years).

Table 1 shows the baseline characteristics of the sample by treated and untreated diabetes status (ever vs. never) in the at-risk sample. On average, compared with those without diabetes, participants with diabetes were slightly younger, more likely to be born in the U.S., and more likely to have a regular medical doctor, which may reflect better access to healthcare among those with diabetes. Years of education did not differ by diabetes status. They were less likely to be current smokers but more likely to have a history of smoking. They were more likely to have hypertension, larger waist circumferences, higher fasting glucose and insulin, and a history of stroke, myocardial infarction, congestive heart failure, intermittent claudication, and kidney disease.

Compared with those with treated diabetes, those with untreated diabetes were more often immigrants and had smaller waists, lower glucose and insulin, less hypertension, and fewer reports of stroke, myocardial infarction, intermittent claudication, and kidney disease.

Among participants with diabetes, 62.2\% met at least two criteria for diabetes in this study (elevated fasting glucose, antidiabetic medication use, or self-report) and 37.8\% met one (13.3% fasting glucose, 3.4% antidiabetic medication use, and 21.1% self-report) (data not shown in tables). Among the participants who reported a physician diagnosis of diabetes at baseline, the median reported duration of diabetes was 10 years (interquartile range 5–20 years). At baseline, 64.7\% of participants with diabetes were using antidiabetic medications: 36.1\% were using one medication and 28.7\% were using two or more medications. Sulfonylureas were the most common class (73\%) of antidiabetic drugs (36). The proportion of patients taking...
antidiabetic medications remained relatively constant throughout follow-up (64.7% in year 1 up to 69% in year 7).

More participants with diabetes died (n = 182, 26.9%) than participants without diabetes (n = 179, 19.0%). In a Cox model, treated and untreated diabetes was associated with increased risk of death after adjustment for sex, education, time-dependent waist circumference, and time-dependent stroke (HR 2.15 [95% CI 1.58–2.95]; 2.12 [1.65–2.73]). There were more deaths among participants with incident dementia/CIND (n = 63, 39.6%) than among those without dementia/CIND (n = 298, 20.4%). Incident dementia/CIND was associated with an increased risk of death in a Cox model adjusted for the same covariates (2.48 [1.75–3.51]).

Table 2 shows the HRs relating time-dependent diabetes to the incidence of dementia/CIND from competing risk models and Cox models. In both types of models, treated diabetes was associated with higher incidence of dementia/CIND than no diabetes. Untreated diabetes was only associated with higher incidence of dementia/CIND in Cox models. Comparison of dementia/CIND risk in treated to untreated diabetes was not significant (HR 1.32 [95% CI 0.80–2.19], P = 0.28). In model 2, adjustment for time-dependent waist circumference, a potential confounder of the association between diabetes and dementia/CIND risk, increased the HRs for treated diabetes and untreated diabetes by 10% and 15%, respectively, compared with the base model (model 1), which adjusted for only age (as time scale), sex, and years of education. In model 3 (fully adjusted model), addition of time-dependent stroke modestly increased the HR for treated diabetes by 9% and untreated diabetes by 10%, but the association with treated diabetes remained strong and statistically significant. Time-dependent stroke did not modify the association between diabetes and dementia/CIND (interaction between stroke and diabetes P = 0.97; data not shown). Compared with the Cox regression model 3, accounting for competing risk of death in model 3 attenuated the HR for treated diabetes by 14% and for untreated diabetes by 18%.

Figure 2 displays the estimated cumulative incidence functions for dementia/CIND by diabetes status from the fully adjusted competing risk regression model (model 3). The graph demonstrates that the incidence of dementia/CIND was highest among those with treated diabetes, followed by people untreated for diabetes and then those without diabetes.

**CONCLUSIONS**—In this 10-year population-based study, we found that those with treated diabetes had a twofold increased risk of dementia/CIND among older Mexican Americans, even after accounting for the competing risk of mortality and changes over time in risk factor exposures. Those with treated diabetes in our sample have higher glucose, insulin, and hypertension and more comorbid cardiovascular disease and may have more severe diabetes than those who were untreated. This may explain why their dementia risk is higher, given that the risk of death is similar in both groups. However, comparison of dementia/CIND risk in treated to untreated diabetes was not statistically significant (HR treated vs. untreated: 1.32, P = 0.28). Standard Cox models that do not incorporate adjustment for competing risk consistently provided a larger estimate of effect.

Previous epidemiologic studies in non-Hispanic white populations have also found that diabetes is associated with a twofold increased risk of dementia (2–13). Most research on the association between diabetes and dementia has been conducted in non-Hispanic white populations, where diabetes burden is lower than among Mexican Americans (16). To our knowledge, this is the first study to evaluate the association between diabetes and dementia or CIND among older Mexican Americans.

In addition to studying a different ethnic group, the current study differs from previous studies because the analysis takes into account the competing risk of death. It is well established that diabetest is associated with higher mortality rates (16), and previous studies have also shown that cognitive decline (22,23) is associated with an increased risk of death. Diabetes-related mortality differentially influences the number of dementia/CIND cases that occur. Since diabetes is associated with death, a standard Cox model, which ignores the competing risk of death, may result in an overestimation of the effect of diabetes on incidence of dementia/CIND (34,37). Although the Cox model treats deaths as censored observations and removes individuals from the denominator for the hazard rate at death, the competing risk model treats death as a competing risk by retaining those who die without dementia in the
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Table 2—HRs (95% CI) from competing risk regression models relating diabetes and incidence of dementia/CIND

|                      | Competing risk models | Cox models |
|----------------------|-----------------------|------------|
|                      | 1.0                   | 1.0        |
| **Model 1**          |                       |            |
| No diabetes (ref)    |                       |            |
| Diabetes untreated   | 1.50 (0.94–2.40)      | 1.93 (1.22–3.07) |
| Diabetes treated     | 2.06 (1.47–2.91)      | 2.38 (1.68–3.37) |
| Female vs. male sex  | 1.35 (0.98–1.86)      | 1.22 (0.88–1.68) |
| Education (years)    | 0.96 (0.93–0.99)      | 0.97 (0.94–1.00) |
| **Model 2**          |                       |            |
| No diabetes (ref)    | 1.0                   | 1.0        |
| Diabetes untreated   | 1.73 (1.05–2.86)      | 2.16 (1.33–3.54) |
| Diabetes treated     | 2.26 (1.57–3.27)      | 2.66 (1.85–3.83) |
| Female vs. male sex  | 1.31 (0.93–1.83)      | 1.14 (0.81–1.61) |
| Education (years)    | 0.96 (0.93–0.99)      | 0.96 (0.93–0.99) |
| Waist circumference (inches) (TD) | 0.97 (0.94–1.00) | 0.96 (0.93–1.00) |
| **Model 3**          |                       |            |
| No diabetes (ref)    | 1.0                   | 1.0        |
| Diabetes untreated   | 1.55 (0.93–2.58)      | 1.88 (1.15–3.07) |
| Diabetes treated     | 2.05 (1.41–2.97)      | 2.38 (1.65–3.44) |
| Female vs. male sex  | 1.30 (0.92–1.82)      | 1.15 (0.82–1.61) |
| Education (years)    | 0.95 (0.92–0.99)      | 0.96 (0.93–0.99) |
| Waist circumference (inches) (TD) | 0.97 (0.94–1.00) | 0.97 (0.93–1.00) |
| Stroke (TD)          | 2.95 (2.04–4.27)      | 3.28 (2.28–4.72) |

Age adjusted for entry age is the time scale in all models. ref, reference; TD, time dependent.

denominator for the hazard rate. In effect, this approach models these individuals as no longer at risk for dementia/CIND. This results in a lower HR than the standard Cox model. The competing risk regression model produces estimates that reflect the actual incidence of dementia/CIND among people with diabetes compared with those without diabetes. This approach may be useful for clinical predictions and for predictions of future dementia/CIND incidence in the population. In this population, accounting for the competing risk of death altered the fully adjusted risk estimates for treated and untreated diabetes by 14 and 18%, respectively. This change is large enough (≥10%) to be considered an important confounder by conventional confounder identification criteria (38).

Figure 2—Cumulative incidence functions for dementia/CIND by diabetes status, accounting for the competing risk of death, from competing risk regression model adjusted for sex, years of education, waist circumference, and stroke. Squares, no diabetes; circles, diabetes untreated; triangles, diabetes treated.

These findings have important implications for prediction of future dementia incidence among Mexican Americans and other racial/ethnic groups. It is important to consider how future changes in mortality rates among people with diabetes may affect dementia rates. A recent publication from the National Health Interview Survey reported that mortality rates among adults with diabetes declined by 23% between 1997 and 2006 (20). This trend was observed in the overall population as well as across age and racial/ethnic subgroups; the decline was greatest among Hispanics (38%). The authors point out that the change in death rates is likely due to multiple factors, including improved diabetes medical care, treatments, and self-management behaviors. In fact, results from the National Health and Nutrition Examination Survey 1999–2008 (39) suggest that blood pressure, glycemic control, LDL cholesterol, and HbA1c have improved in Mexican Americans as well as other groups. These improvements may propel the decline in mortality rates observed over the same period. These changes have important public health implications for future incidence of dementia/CIND in the population. The potential impact on dementia/CIND incidence among people with diabetes will depend on the factors causing the decline in the mortality rate. If mortality rates among those with diabetes decline due to earlier screening and improved management and therefore decreases in disease progression and severity, dementia/CIND rates among people with diabetes might also decrease. If mortality rates decline among those with diabetes without reducing disease severity, and if more severe diabetes influences dementia risk, dementia/CIND rates among people with diabetes could potentially increase.

SALSA is a population-based study. The sample is representative of older Latinos residing in the Sacramento area in California in 1998–1999 (24). The risk estimates from this study are generalizable to populations with similar characteristics, including similar mortality rates. In this population, diabetes was associated with over a twofold increased risk of death. Mortality associated with diabetes is slightly higher in our population than in two recent nationally representative studies: the National Health Interview Survey (20) and the Cancer Prevention Study-II (21). In both of these studies, diabetes was associated with a nearly twofold increased risk of death.

A major strength of this study is the large sample and population-based longitudinal design, which enabled us to study incident dementia/CIND over a long time period in an understudied ethnic group with a high burden of diabetes. This is the only population-based study of clinically assessed dementia in Mexican Americans. Because our analysis accounted for the competing risk of death, our results can be interpreted as the absolute risk of dementia/CIND among people with diabetes compared with those without, making our results relevant for clinical decision making and public health predictions.

This study also has some limitations. As for any study of older adults, individuals had to survive at least to 60 years of age to participate in this study. Selection due to premature mortality among people with diabetes before 60 years of age may have occurred and affected the risk estimate in our sample. Mortality was the primary source of attrition, but some
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E.R.M. developed the study concept, analyzed and interpreted the data, and drafted and revised the manuscript. M.N.H. obtained funding, developed the study concept, collected and interpreted data, supervised, and revised the manuscript. A.M.K. contributed to the study concept and revised the manuscript. K.Y. contributed to the study concept and revised the manuscript. J.N. developed the study concept, interpreted the data, and revised the manuscript. M.N.H. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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nonmortality attrition was present. Participants with diabetes and participants experiencing symptoms of dementia/ CIND may have been more likely to drop out of the study than healthier participants, which could have biased our results toward the null. Stroke was measured by self-report of a physician diagnosis, which is likely to underestimate the presence of strokes, especially “silent strokes.” This would tend to attenuate the association between stroke and dementia because undiagnosed strokes are included in the nonstroke category. To the extent to which stroke is on the pathway between diabetes and dementia, such misclassification may reduce the influence of adjustment for stroke on that association. Physical activity was estimated by self-reported outdoor walking speed, which may underestimate physical activity levels. As in all observational studies, we cannot rule out the possibility of residual confounding, particularly from unmeasured behavioral factors.

In conclusion, we found that treated type 2 diabetes is associated with a twofold increased incidence of dementia/ CIND in older Mexican Americans, even after accounting for the competing risk of mortality. Screening and treatment for diabetes that change survival among those with type 2 diabetes may influence future dementia incidence rates. Cognitive screening in those with diabetes is warranted by the preponderance of evidence supporting a robust link between diabetes and dementia.
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