Tuberculosis and Diabetes in Southern Mexico

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OBJECTIVE — To determine the impact of diabetes on the rates of tuberculosis in a region where both diseases are prevalent.

RESEARCH DESIGN AND METHODS — Data from a population-based cohort of patients with pulmonary tuberculosis undergoing clinical and mycobacteriologic evaluation (isolation, identification, drug-susceptibility testing, and IS6110-based genotyping and spoligotyping) were linked to the 2000 National Health Survey (ENSA2000), a national probabilistic, polystage, stratified, cluster household survey of the civilian, noninstitutionalized population of Mexico.

RESULTS — From March 1995 to March 2003, 581 patients with Mycobacterium tuberculosis culture and fingerprint were diagnosed, 29.6% of whom had been diagnosed previously with diabetes by a physician. According to the ENSA2000, the estimated prevalence of diabetes in the study area was 5.3% (95% CI 4.1–6.5). The estimated rates of tuberculosis for the study area were greater for patients with diabetes than for nondiabetic individuals (209.5 vs. 30.7 per 100,000 person-years, $P < 0.0001$).

CONCLUSIONS — In this setting, the rate of tuberculosis was increased 6.8-fold (95% CI 5.7–8.2, $P < 0.0001$) in patients with diabetes due to increases in both reactivated and recently transmitted infection. Comorbidity with diabetes may increase tuberculosis rates as much as coinfection with human immunodeficiency virus (HIV), with important implications for the allocation of health care resources.

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It has been postulated that in the context of economic development, a country's health issues will evolve from infectious to noninfectious diseases. In reality, this transition more commonly simply adds chronic conditions to a public health system already burdened by infectious diseases (1). In many settings, this process will result in the convergence of two epidemics: diabetes and tuberculosis.

In Mexico, both diabetes and tuberculosis are major public health problems. Diabetes has had a growing trend in previous years, increasing from 6.7% among the adult population in 1993 to 8.18% in 2000 (2). Tuberculosis remains problematic; the estimated case rate is 50 of 100,000 inhabitants (3).

Previous clinic-based studies in developed countries (4,5) demonstrated an association between tuberculosis and diabetes but did not determine whether this is due to an increase in recently transmitted or reactivated infection of tuberculosis. We now report the results of a population-based molecular epidemiologic study of tuberculosis among persons with and without diabetes in a developing country. We linked the results of this population-based study with those obtained from the 2000 National Health Survey (ENSA2000) to estimate the relative risk of on going transmission and reactivation of tuberculosis among diabetic and nondiabetic population resident of the study area. Because this community typifies communities that are undergoing health care transition, these results have general applicability.

RESEARCH DESIGN AND METHODS

ENSA2000

ENSA2000 was a probabilistic, multistage, stratified, cluster household survey conducted by the Mexican Secretariat of Health from November 1999 to June 2000. Research design and methods have been described previously (2). As part of this survey, 1,334 individuals were randomly selected in the state of Veracruz to be representative of the civilian, noninstitutionalized population at the state level. The study was performed in accordance with the Helsinki Declaration of Human Studies.

Population-based tuberculosis study

Study site and enrollment procedures have been described previously (6). The study area included 12 municipalities in the Orizaba Health Jurisdiction, state of Veracruz, Mexico, which encompassed 618.11 km^2 and 369,235 inhabitants, of whom 14.9% were living in rural communities (7). Tuberculosis incidence rates during 2000 for the state (28.0 of 100,000 inhabitants) were higher than national rates (15.9 of 100,000 inhabitants) (8).

Community-based screening of individuals with chronic cough (>2 weeks) was performed between March 1995 and

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Abbreviations: ENSA2000, 2000 National Health Survey; RFLP, restriction fragment–length polymorphism.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

April 2003. Health promoters were trained in prevention and control measures of the main health programs identified by the National Health Program of the Mexican government (cholera and other infectious diarrheas, acute respiratory infections, pulmonary tuberculosis, dengue, hypertension and diabetes, children vaccination, nutrition, reproductive health, and basic sanitation). Adult patients (>19 years of age) with positive results of acid-fast bacilli sputum smear or positive culture underwent epidemiologic, clinical (standardized questionnaire, physical examination, chest x-ray study, human immunodeficiency virus [HIV] test), and mycobacteriologic evaluation. Treatment was provided in accordance with official norms (9). Informed consent was obtained from participants. The study was approved by appropriate institutional review boards.

Mycobacteriologic and genotyping tests

Sputum samples were processed for Mycobacterium tuberculosis following standardized procedures (10). Isolates were genotyped and compared using IS6110-based restriction fragment–length polymorphisms (RFLPs) and spoligotyping if the isolate's IS6110 RFLP patterns had fewer than six bands, as previously described (9).

Measurement of glucose concentration

Measurement of capillary glucose concentration was performed in participants of the ENSA2000 using an Accutrend sensor monitor (Roche Diagnostics, Montclair, NJ). For 90.4% of the patients with tuberculosis (525 of 581) recruited by the population-based tuberculosis study, for whom a serum sample obtained after the diagnosis of tuberculosis was available, serum glucose determination was performed using Synchron CX5 Delta equipment (Beckman Coulter, Fullerton, CA) (11). Both methods have been found to correlate closely: within-run coefficients of variation between both methods have been 15.2, 5, and 1.2% at concentrations of 0.9, 4.2, and 19.6 mmol/l, respectively; and 96% of the Accutrend Sensor results have been found within 15% of the comparison method results (12). The same cutoff level was used for both capillary and venous blood samples.

Definitions

We used two definitions of diabetes. In the first, diabetes status was considered present among individuals who had received a previous diagnosis by a physician. Because this definition has the limitation of underestimation of the real frequency because of undiagnosed diabetes, for sensitivity analysis, a second definition was used. For the second definition, in addition to previous diagnosis, blood glucose levels (≥126 mg/dl in fasting samples or ≥200 mg/dl for random samples) were considered (13). To prevent information bias, information regarding diabetes status (both clinical and blood glucose measurement) was elicited in the same way for participants in the ENSA2000 and in the tuberculosis study.

We used an established molecular epidemiologic technique to classify patients as having tuberculosis as a consequence of reactivation of a latent tuberculosis infection or recently transmitted infection (14). In brief, cases were considered "clustered" if two or more patients diagnosed within a year of each other were infected with the same strain (as defined by IS6110-based RFLP and spoligotyping). We assumed that clustered cases represented recently transmitted infection and that tuberculosis cases with a unique DNA fingerprint pattern arose from the reactivation of a latent tuberculosis infection.

Sensitivity analysis

We considered several sources of biases. We compared characteristics of consenting and nonconsenting patients. Because we were unable to study all bacteriologically confirmed patients, we performed sensitivity analysis for unidentified case bias. First, because missing case subjects could belong to the 23% of patients for whom a DNA fingerprint was unavailable, we compared patient variables associated with presence or absence of DNA fingerprints. Second, to study the potential impact of partial sampling (individuals who contributed to the transmission of tuberculosis in the study area but were not part of the study population), we performed two statistical studies. In the first, we randomly deleted 10, 20, 30, 40, and 50% of the cases and recalculated the ratio of rates of tuberculosis among diabetic and nondiabetic individuals at each level. Second, we successively removed clusters beginning in 1995, 1996, 1997, 1998, 1999, 2000, 2001, and 2002, redoing the analysis at the end of each year.

The second source of bias was based on our definition of diabetes status. First, we reasoned that because our diagnosis of diabetes was based solely on previous diagnosis of diabetes by a physician, some of the patients with diabetes might have been misclassified as nondiabetic subjects. We recalculated the ratio of incidence rates for diabetic and nondiabetic populations based on both previous diagnosis of diabetes and glucose determination for 90.4% of our study population (525 of 581 subjects). Second, because it has been determined that a proportion of patients with active tuberculosis have impaired glucose tolerance, which improves or returns to levels before the tuberculosis disease after receiving effective tuberculosis treatment, we repeated the analyses considering as nondiabetic those patients who might have had glucose intolerance after diagnosis of diabetes (patients who had not been previously diagnosed with diabetes but had abnormal glucose levels when diagnosed with active tuberculosis and patients who were diagnosed after initiation of tuberculosis symptoms).

Finally, we also tested the possibility that our definition of time between diagnoses dates of successive matching fingerprints could affect our findings, as has been described (15). We analyzed the ratio of rates of tuberculosis among diabetic and nondiabetic populations, modifying the time between diagnosis dates of successive matching fingerprints to 6, 18, 24, 30, and 36 months.

Analysis

Because the ENSA2000 uses stratified probability samples, all observations were weighted by the sample weights, which consisted of the reciprocals of the sampling probabilities, adjusted for nonresponse and poststratification by age and sex. The SE estimated obtained from weighted analysis in the Statistical Analysis System was adjusted by the average design effects (a ratio of the variance from a cluster sample to that from a simple random sample of the same size) for prevalence generated from SUDAAN 7.5.6 Software for Survey Data Analysis (Research Triangle Institute, Research Triangle Park, NC) and averaged across sex and 5-year age categories (16).

We estimated the prevalence of diabetes of the study site in the Health Juris-

Table 1—*Sociodemographic, clinical, bacteriologic, and therapeutic characteristics of patients with pulmonary tuberculosis according to diagnosis of diabetes, Orizaba, Veracruz, 1995–2003*

	Total population	Diabetic patients	Nondiabetic patients	*P**
n	581	172	409	
Sociodemographic				
Household visit to invite participation	32	23.5	35.6	<0.0001
Age (years)	44 (19–86)	53 (23–82)	39 (19–86)	<0.0001
Men	59.9	55.2	61.9	0.1
Indigenous origin	23.2	18.0	25.4	0.05
Rural and industrial workers	22.9	15.7	25.9	0.007
Bacille Calmette-Guérin scar	44.2	30.8	49.9	<0.0001
Previous hospitalization	50.4	62.8	45.2	<0.0001
Residence in shelters	3.8	0.0	5.4	0.002
Social security	34.9	51.7	27.9	<0.0001
Alcohol use	47.7	40.7	50.6	0.02
Household crowding	36.3	28.1	39.0	0.01
Household with earthen floor	19.7	11.9	23.0	0.002
Clinical				
HIV infection	2.7	1.2	3.3	0.2
BMI (<18 kg/m^2)	22.8	8.1	28.9	<0.0001
Hemoptysis	32.9	34.5	32.3	0.6
Fever	75.9	77.9	75.1	0.5
Cavities	35.8	42.8	32.9	0.02
Interval between initiation of symptoms and treatment (days)	104 (3–3,248)	99 (4–1,569)	109 (3–3,248)	0.8
Bacteriologic				
Resistance to isoniazid and rifampin	5.7	8.1	4.7	0.1
Other resistance	14.5	14.0	14.7	0.8
Treatment outcome				
Cure	82.7	82.4	82.9	0.9
Failure	2.5	4.8	1.5	0.02
Default	9.9	9.1	10.2	0.7
Retreatment	7.0	9.3	6.1	0.2
All-cause mortality	16.4	19.8	14.9	0.1
Death from tuberculosis	7.9	5.8	8.8	0.2
Death from other causes	8.4	14.0	2.4	0.001

Data are % or median (range). *For comparison between diabetic and nondiabetic patients; χ^2 and Wilcoxon's tests were used.

diction of Orizaba along with its 95% CI according to age and adjusted by sex by means of the usual Mantel-Haenszel procedure. Estimations were based on the prevalence rate and CI of diabetes for the population of the state of Veracruz. Population data for the state and the study area were obtained from the 1995 population count (17) and the 2000 census (7).

The incidence rates of pulmonary tuberculosis (all, reactivated, and recently transmitted infection) among diabetic and nondiabetic subjects for the study site were calculated using diabetic or nondiabetic tuberculosis patients recruited in the tuberculosis study as numerators and estimation of the diabetic and nondiabetic adult population (aged >19 years) for the study area from the ENSA2000 as denominators. The ratio of diabetic to nondiabetic incidence rates (relative risk) of tuberculosis was calculated, and 95% CI was estimated. Statistical significance was calculated using the Mantel-Haenszel χ^2 test. Population-attributable percentage of risk for tuberculosis due to diabetes was calculated.

DBASE IV and STATA 7.0 software programs (Stata, Santa Monica, CA) were used for data analysis.

RESULTS — Of a total of 6,793 persons presenting with cough, 775 (11.4%) patients with bacteriologically confirmed pulmonary tuberculosis were diagnosed between March 1995 and March 2003. Of these, 755 patients consented to participate. Comparison between consenting and nonconsenting individuals showed that both groups were similar regarding age, sex, urban/rural residence, clinical symptoms, and bacilli concentration in sputum samples. An adequate fingerprint was available for 581 (76.9%) tuberculosis patients, who represent the study population.

Of the 581 patients, 29.6% (172 of 581) had been previously diagnosed with diabetes by a physician. A total of 22% of these patients (38 of 172) had previously used insulin at least once. HIV infection was investigated among 96.9% (563 of 581) subjects; 15 (2.7%) were found to be HIV infected. Comparison of sociodemographic, clinical, and therapeutic characteristics for diabetic and nondiabetic patients is shown in Table 1.

Table 2—*Incidence rates (per 100,000 person-years) among diabetic and nondiabetic populations (clustering within 1 year of diagnosis)*

Age-group (years)	TB patients with diabetes (*n*)	Incidence rate of TB among diabetic population	TB patients without diabetes (*n*)	Incidence rate of TB among nondiabetic population	Ratio of rates (95% CI)	*P*	Population attributable risk (%)
Clustered cases							
20–44	18	127.3	62	6.9	18.6 (10.3–31.8)	<0.0001	21
45–64	15	39.3	25	8.0	4.9 (2.4–9.6)	<0.0001	29
65–89	9	30.2	12	10.1	3.0 (1.1–7.8)	0.01	28
Total	42	51.2	99	7.4	6.9 (4.7–9.9)	<0.0001	25
Reactivated cases							
20–44	25	176.8	192	21.2	8.3 (5.3–12.7)	<0.0001	10
45–64	78	204.1	75	24.1	8.5 (6.0–11.8)	<0.0001	44
65–89	27	90.7	43	36.1	2.5 (1.5- 4.2)	0.0004	23
Total	130	158.3	310	23.2	6.8 (5.5–8.4)	<0.0001	25
Total cases							
20–44	43	304.2	254	28.1	10.8 (7.6–14.9)	<0.0001	13
45–64	93	243.4	100	32.2	7.6 (5.6–10.1)	<0.0001	41
65–89	36	121.0	55	46.2	2.6 (1.7–4.0)	<0.0001	24
Total	172	209.5	409	30.7	6.8 (5.7–8.2)	<0.0001	25

TB, tuberculosis.

The ENSA2000 studied 1,334 individuals selected from the 3,287,194 adult residents of the state of Veracruz. Of these, 97 (7.2%) had been previously diagnosed with diabetes. After adjustment for design effect, estimated prevalence of diabetes adjusted by sex for the adult population of the study area was 5.3% (95% CI 4.1–6.5). Therefore, of the 212,310 adult residents of the study area, it was estimated that the number of diabetic patients was 11,274 (95% CI 8,705–13,800).

As shown in Table 2, the incidence rate of tuberculosis was significantly greater among the diabetic individuals than among the nondiabetic population (209.5 vs. 30.7 per 100,000 person-years, $P < 0.0001$). The overall ratio of incidence rates for the diabetic and nondiabetic population was 6.8 (95% CI 5.7–8.2). The ratio of tuberculosis rates among diabetic and nondiabetic populations was above unity both for recently transmitted disease and for reactivated disease for all age-groups.

Based on the population-attributable risk, the proportion of tuberculosis attributable to diabetes was higher for the 45- to 64-year age-group. Overall, risk of tuberculosis attributable to diabetes was 25%. Therefore, this proportion of all patients with tuberculosis could be avoided if tuberculosis among diabetic patients could be prevented by treating latent infections and interrupting transmission (Table 2).

Sensitivity analysis

Missing cases bias. A total of 23% of patients (174 of 755) who were bacteriologically confirmed did not have fingerprints. On bivariate analysis, the absence of a DNA fingerprint was significantly associated with older age (median 47.5 [range 19–86] vs. 44 [19–86] years; $P = 0.03$) and less radiologic damage (22.7% [37 of 163] vs. 35.8% [194 of 542] had cavities; $P = 0.002$). Other sociodemographic characteristics such as sex, access to social security, and household characteristics were similar between both groups. Characteristics that had been found to be associated with transmission in previous studies, such as rural residence, ethnicity, and alcohol use, were distributed similarly between both groups. Random elimination of data showed that undersampling would not be expected to bias this estimate (Fig. 1*A*). Exclusion of clusters beginning in each of the years from 1995 to 2002 showed that the ratio of incidence rates for diabetic and nondiabetic populations remained relatively stable, although the CI increased, particularly when the number of clusters decreased during the most recent years (Fig. 1*B*).

Misclassification bias. We performed glucose determination on 90.4% of the tuberculosis patients (525 of 581) for whom a serum sample was available. We found that 13 individuals with no previous diagnosis of diabetes had elevated glucose levels and had, therefore, been classified as nondiabetic patients in our previous analysis. Using both criteria (previous diagnosis and elevated glucose determination), prevalence of diabetes for the cohort of tuberculosis patients was 35.2% (185 of 525). After adjustment for design effect, estimated prevalence of diabetes using both criteria adjusted by sex for the adult population of the study area was 7.61% (95% CI 6.06–9.2). The ratio of incidence rates for diabetic and nondiabetic populations, based on both criteria, continued to be higher for diabetic patients for all types of tuberculosis: clustered cases 6.4 (4.3–9.4), $P < 0.0001$; reactivated cases 5.9 (4.8–7.3), $P < 0.0001$; and total cases 6.0 (5.0–7.2), $P < 0.0001$. A total of 41 patients might have had glucose intolerance due to tuberculosis (13 not previously diagnosed with diabetes, 28 diagnosed after initiation of tuberculosis symptoms). When these 41 patients were classified as nondiabetic patients, the ratio of incidence rates for diabetic and nondiabetic populations continued to be higher in diabetic patients for all types of tuberculosis: clustered cases 4.4 (2.9–6.5), $P < 0.0001$; reactivated cases 4.6 (3.7–5.7), $P <$

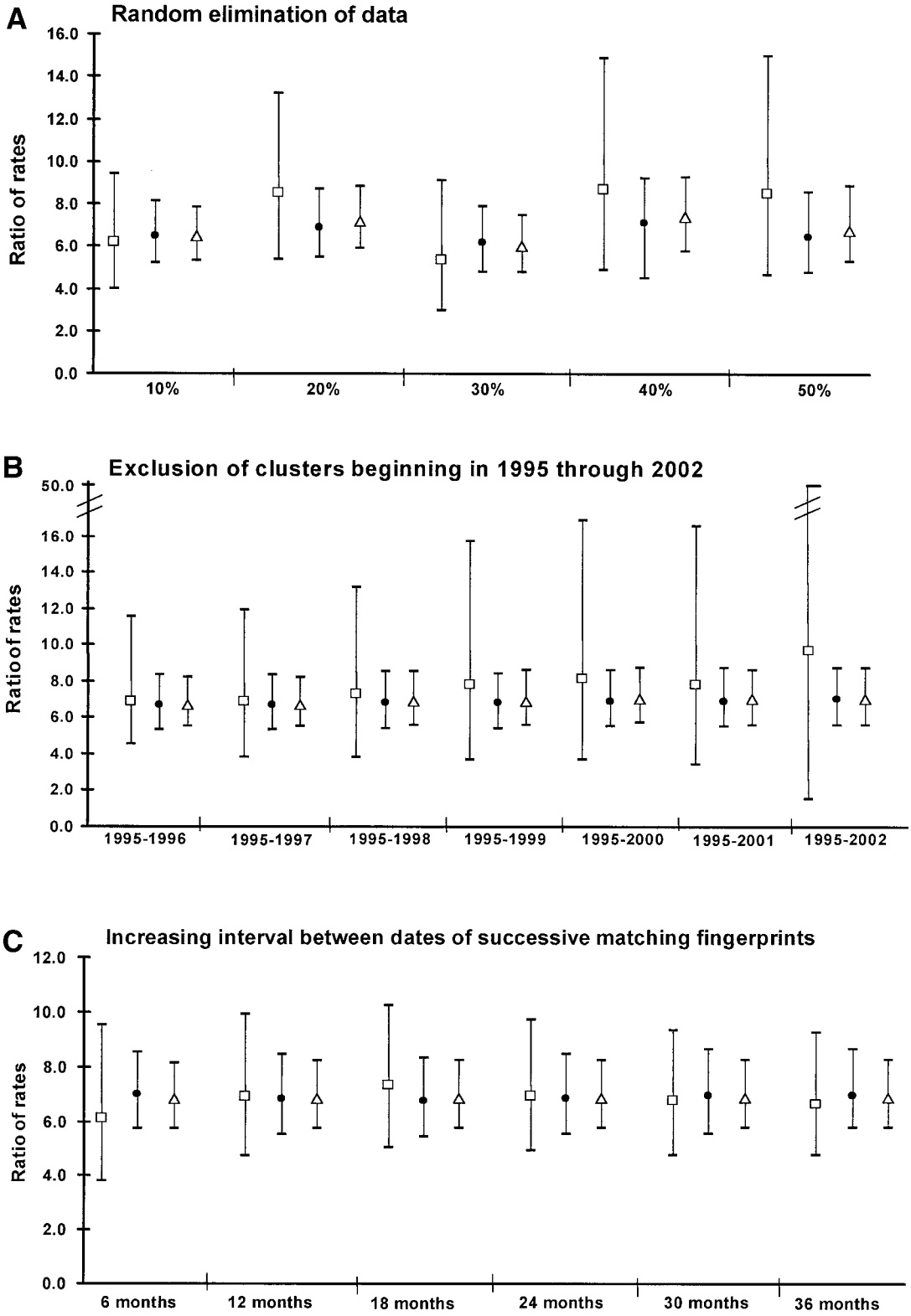

Figure 1—*Impact of undersampling and increase in interval between dates of successive matching fingerprints on the estimate of the ratio of incidence rates for the diabetic and nondiabetic populations for clustered cases (□), reactivated cases (●), and total cases (△). A: Random deletion of 10, 20, 30, 40, and 50% showed that the undersampling would not be expected to bias the estimate of the ratio of rates of tuberculosis among diabetic and nondiabetic populations. B: Exclusion of clusters beginning in each of the years from 1995 to 2002 showed that the ratio of incidence rates for the diabetic and nondiabetic populations remained relatively stable, although the CI increased, particularly when the number of clusters decreased during the most recent years. C: Increase in the interval between dates of successive matching fingerprints had no impact on the estimate for the ratio of incidence rates for the diabetic and nondiabetic populations.*

0.0001; and total cases 4.5 (3.7–5.5), $P < 0.0001$.

Finally, increasing the interval between dates of successive matching fingerprints had no impact on the estimate for the ratio of incidence rates for diabetic and nondiabetic populations (Fig. 1*C*).

CONCLUSIONS — Many studies have explored the association between diabetes and tuberculosis. In developed countries, studies dating to the first half of the past century demonstrated considerable increase in the frequency of tuberculosis among patients with diabetes (4,5,18), although the proportion with comorbidity has ranged widely from 1.0 (19) to 9.3% (20). Other studies have shown a higher frequency of diabetes among individuals with tuberculosis (21,22). Similar results were found in the few studies that have addressed this association in developing countries (23,24). However, with one exception, these studies have been clinic or hospital based, and therefore, it is difficult to extrapolate their findings to the general population (25). Furthermore, none of these studies were able to determine whether the increased risk of tuberculosis among patients with diabetes was due to recently transmitted or reactivated disease.

We now report a prospective, population-based evaluation of tuberculosis in a community in Southern Mexico that is typical of the health care transition being experienced by much of Latin America. In this setting, the rate of tuberculosis increased sevenfold among individuals with diabetes. In addition, incorporation of molecular epidemiologic techniques allowed us to show that this increase is due to both reactivation and recently transmitted infection.

This study has several possible sources of bias. Households with diabetic patients may have been preferentially visited by health promoters. We consider this unlikely because health promoters participate in a number of government health programs and, being charged with a broad spectrum of infectious and chronic diseases, do not specifically target diabetes. Moreover, as shown in Table 1, nondiabetic patients had a greater probability of receiving a household visit to invite participation. Additionally, a bias might have been introduced if tuberculosis patients with diabetes had a higher rate of agreeing to participate in the study than tuberculosis patients without diabetes. We consider that this was improbable, because we were unable to detect sociodemographic and clinical differences between participants and nonparticipants. We were not successful in performing RFLP on all case subjects, and therefore, the proportion of isolates belonging to clusters is subject to error, particularly among older individuals and patients with less radiologic damage. To study the impact of missed cases registered outside our study area or before we began our study, we performed two simulations of data loss. We randomly removed data and we removed clusters beginning in successive years. As shown in Fig. 1, these methods did not significantly alter the estimate of the ratio of rates of tuberculosis among diabetic and nondiabetic patients. Another possible bias is that the diagnosis of diabetes among patients with tuberculosis was based on information provided by the patient. This method has been found to be adequate for epidemiologic studies among Hispanics in the U.S. (26). Restricted analysis using both previous diagnosis and glucose determination demonstrated that the rate of tuberculosis continued to be increased sixfold (95% CI 5.0–7.2) in individuals with diabetes. Rates for patients with diabetes continued to be increased when the possibility of a false diagnosis of diabetes was considered for patients who might have had glucose intolerance as a consequence of tuberculosis disease. Because there were significant socioeconomic differences noted between diabetic and nondiabetic patients, it is possible that persons with better access to health care services were more likely to be diagnosed with both diabetes and tuberculosis. However, in this study, patients with tuberculosis were actively sought, and prior analysis has shown tuberculosis to be more commonly diagnosed in individuals of lower socioeconomic status (27). Therefore, there was no differential opportunity for diagnosis of tuberculosis according to availability of health services. Finally, our selection of the time interval allowed us to consider tuberculosis that was transmitted very recently and progressed to disease. The validity of using a 1-year interval was confirmed with the sensitivity analysis using different time periods, because our estimate for the ratio of rates persisted despite modification of the time interval.

The magnitude of the increased risk attributable to diabetes in this population has important implications for prioritization of health care. The increased likelihood of tuberculosis due to diabetes is comparable to what has been found in other studies attributable to coinfection with HIV. However, because the rates of diabetes are so much greater than the rates of HIV in this community, the actual impact of diabetes on the incidence of tuberculosis is much greater than that of HIV. Results from the ENSA2000 have shown that for all of Mexico, prevalence of HIV infection among individuals aged >15 years is 0.1% (28), whereas prevalence of diabetes is of 8.18% (1). When HIV prevalence in the study area was estimated based on national HIV prevalence, tuberculosis-attributable risk due to HIV was 2%, compared with 25% due to diabetes. Therefore, although in many parts of the world it may be appropriate to lavish resources on tuberculosis and HIV, attention to the interactions of tuberculosis and diabetes may yield greater benefits for other regions.

Our finding that both ongoing transmission and reactivation contribute significantly to disease has important implications for approaches to enhance directly observed therapy, short course–based tuberculosis control programs. Because transmission of the bacilli and rapid progression of disease contribute significantly, directly observed therapy, short course–based efforts to interrupt transmission with prompt diagnosis and therapy must be prioritized. However, the realization that reactivation of latent infection also contributes significantly suggests that there may be benefits derived from targeted tuberculin skin testing and treatment of latent tuberculosis infection in diabetic patients residing in developing countries.

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