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Cause-specific mortality in diabetes: Retrospective hospital based data from south India

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Abstract

Background: India lacks comprehensive mortality data in individuals with diabetes. The present retrospective case-control study compared the causes of death in diabetic and non-diabetic inpatients in a tertiary care hospital in 2007.

Methods: Deaths in diabetic patients (n = 315) were compared with 307 randomly selected controls. Medical chart review established the primary cause of death, demographics, and clinical data. Data were summarized using descriptive statistics and comparative analyses were performed.

Results: Of the 79 067 inpatient admissions during 2007, diabetes of any type was recorded for 6517 (8.2%). There were 2017 inpatient deaths registered, 315 (15.6%) in diabetic patients and 1702 (84.4%) in non-diabetic patients, corresponding to mortality rates of 48.3/1000 admissions for diabetic patients and 23.4/1000 admissions for non-diabetic patients. The mean duration of hospitalization prior to death in diabetic versus non-diabetic patients was 6.4 vs 7.7 days (P = 0.015). Causes of death in diabetic patients were vascular disease (38.4%), infection (34.3%), renal failure (8.9%), and malignancy (8.9%); diabetic patients had significantly higher odds of death from vascular disease (odds ratio [OR] 4.05, 95% confidence interval [CI] 2.67–6.16; $P \leq 0.0001$), renal causes (OR 7.39, 95%CI 2.53–29.27; $P \leq 0.001$) and infection (OR 1.61, 95% CI 1.12–2.32; $P \leq 0.0001$). Comparing cases and controls after stratifying by age (<56 and ≥ 56 years), the greater odds of vascular death among diabetics remained significant in both age categories.

Conclusions: We report vascular disease as the leading cause of death among diabetic hospital inpatients in one tertiary care center in India, in contrast with previous hospital-based studies from India.

Keywords: diabetes, India, mortality, vascular deaths.

Significant findings of the study: Mortality rates are higher in diabetics compared with non-diabetics and vascular disease is the leading cause of death among diabetic inpatients in India, contrary to previous hospital-based data that reported infectious disease as the primary cause of death among diabetics.
What this study adds: Knowledge about the changing trends in mortality patterns is an important characteristic of the diabetes epidemic in India; the shift to vascular causes from infectious disease is important information for health policy makers.

ASIA TRACK

Introduction

Diabetes mellitus, which was once considered to be a disease of the wealthy, is now emerging as a health threat in the developing world, with India and China leading the global chart of diabetes prevalence. Of the estimated 285 million people worldwide with diabetes in 2010, approximately 70% live in lower- and middle-income group countries.[1–3] The global burden of diabetes is expected to reach 439 million by the 2030,[3] with the highest rates of growth in the developing world. India is the country with the dubious distinction of having the largest number of people living with diabetes, estimated to be 50.8 million in 2010, a number that is expected to rise to 87.0 million by the 2030.[4]

In addition to the major impact diabetes has on productivity and quality of life, it also carries a higher burden of premature mortality. Comprehensive mortality data are lacking in India and the estimated number of deaths attributable to diabetes may vary widely. The Indian Council of Medical Research has estimated that there were 109 000 deaths annually due to diabetes in India in 2004 (http://sancd.org/uploads/pdf/factsheet_diabetes.pdf, accessed 8 November 2011), but the International Diabetes Federation suggested just a few years later that the number may be far higher, estimating 1 008 000 deaths to be attributable to diabetes in India in the 2010.[5]

The vast majority of deaths in diabetic patients in North America and Europe have been due to cardiovascular and cerebrovascular disease.[6–11] In contrast, in the developing world, infections generally figure more prominently in diabetic mortality. Although earlier studies did report vascular disease as the leading cause of death in diabetics in India,[12–15] better retrospective hospital-based studies in recent years have reported infection to be the most common cause of death among inpatients with diabetes.[16–18] The Chennai Urban Population study (CUPS) from south India found that 52.9% of deaths were due chiefly to cardiovascular causes.[19]

As India works to confront its diabetes epidemic, continuing data on mortality trends will help policy makers and hospitals to plan appropriate secondary and tertiary prevention strategies based on common causes of mortality among diabetics. Therefore, in the aim of the present study was to establish the mortality patterns in patients with diabetes who were admitted to a tertiary care referral center in southern India.

Methods

The present study was a retrospective case-control study using electronic hospital records and death registries from the Medical Records department of Christian Medical College (CMC), Vellore. The institutional ethics committee and review board approved the study.

Hospital setting

The CMC hospital is a 2700-bed tertiary care university hospital located in Vellore, south India. The hospital caters for approximately 1.6 million outpatients every year who come from Vellore town and other parts of the country; hence, the clientele provided for are multidenominational and multi-ethnic in nature.

Subject data retrieval

For the present study, ''diabetes mellitus'' was defined to include any diagnosis of diabetes with ICD-10 codes E10–E14; cases of diabetes during pregnancy (ICD-10 code O24) were excluded. The Medical Records department provided aggregate numbers for the total number of admissions, which included patients admitted with a diagnosis of diabetes mellitus (Fig. 1). From the total number of admissions, 2017 total deaths (315 diabetic deaths and 1702 non-diabetic deaths) were recorded at CMC during the period 1 January–31 December 2007. The hospital records were retrieved for all patients with diabetes mellitus listed anywhere on the death certificate and data regarding age, gender, primary cause of death, length of hospital stay, and HbA1c at admission (where available) were gathered. The primary causes of death were classified as follows: vascular (coronary artery disease, cerebrovascular accident); infectious (urosepsis, pneumonia, tuberculosis [TB], HIV, necrotizing fasciitis, septicemia, diabetic foot, and other infections); renal failure; respiratory failure; liver failure; hyperosmolar coma; diabetic ketoacidosis; malignancy; and road traffic accidents. The relatively smaller number of deaths that were due to rheumatic heart disease, pulmonary thromboembolism, collagen vascular disease, hematological disorders, aneurysm rupture, perforation of the viscera, poisoning, and burns were categorized as ''other''. Systematic random sampling was used to select 307 non-diabetic patients who were admitted for various diseases (other than diabetes) and had inpatient deaths during 2007 as controls.

Statistical analysis

The sample size was calculated by assuming the prevalence of diabetes deaths as 14%, based on previous CMC inpatient mortality statistics from 1999 to 2008.

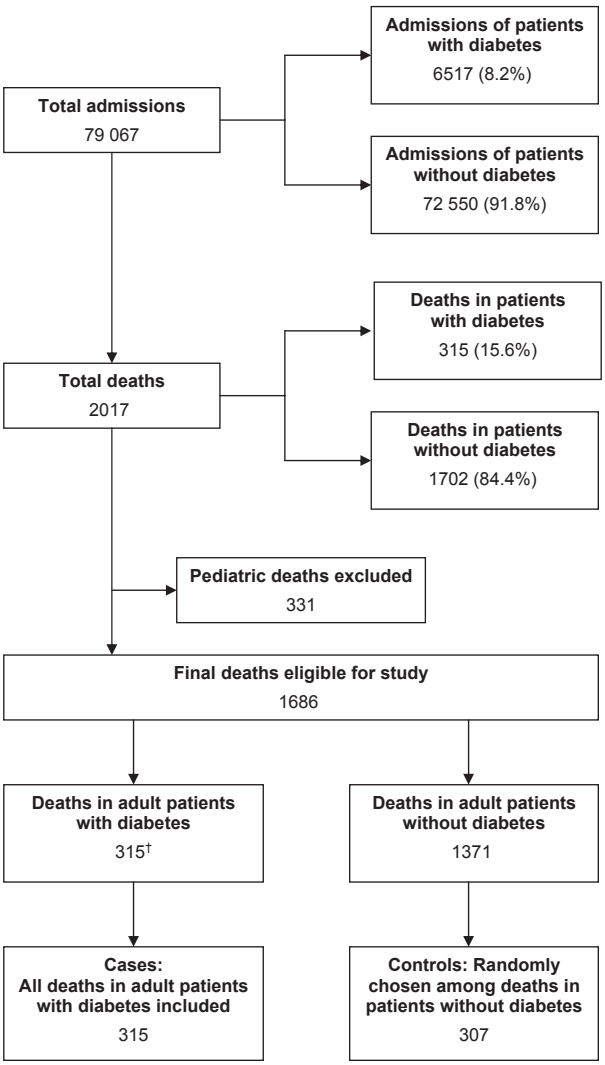

Figure 1 Admission census, mortality, and patient enrollment at Christian Medical College, Vellore, India, in 2007. †No deaths were recorded in pediatric patients with diabetes in 2007.

With a precision of 4% and a 95% confidence interval (CI), the calculated sample size was 301. Because 315 patients with diabetes died during 2007, a decision was made to include all these patients as cases and to compare them with 307 age- and gender-matched non-diabetic controls. The study sample was summarized using descriptive statistics. A comparative analysis was performed using either the Chi-squared test or *t*-test, as appropriate. The strength of the association between diabetic mortality and various causes was calculated using odds ratios (OR) with 95% CI. For stratified analyses (age and sex), adjusted estimates of ORs and 95% CIs were obtained using the Mantel–Haenszel method. Two-tailed *P*-values were calculated. Data were analyzed using SPSS (version 11; SPSS, Chicago, IL, USA).

Results

The total number of inpatient admissions in 2007 was 79 067 (17 828 pediatric; 61 239 adult). Diabetes mellitus was recorded in 6517 (8.2%) of these admissions (4317 [66.2%] men and 2200 [33.8%] women). Of the total 2017 inpatient deaths registered during the study period, 15.6% patients were identified as having diabetes mellitus and 84.4% were non-diabetic deaths, thus representing a mortality rate of 48.3 per 1000 admissions for diabetic patients compared with 23.4 per 1000 admissions for non-diabetic patients. The aggregate hospital data and recruitment of subjects are outlined in Fig. 1.

Among the cases, 65.7% of deaths were in men and 34.2% were in women; in the control group, 61.6% of deaths were in men and 38.4% were in women ($P = 0.28$). Diabetic deaths occurred at a significantly older mean age than in the control group (60.5 ± 11.0 vs 50.2 ± 15.4 years, respectively; $P \leq 0.001$). Among both cases and controls, women died at an earlier age than men (58.01 ± 11.63 vs 61.9 ± 10.9 years, respectively, in cases; 46.4 ± 15.3 vs 52.6 ± 14.9 years, respectively, in controls). The mean duration of hospitalization prior to death in cases and controls was 6.4 ± 1.2 and 7.7 ± 1.1 days, respectively ($P = 0.015$).

The primary causes of death recorded on the death certificates among cases and controls are listed in Table 1. The leading cause of death among patients with diabetes was vascular disease (38.4%), followed by infection (34.3%), renal failure (8.9%), and malignancy (8.9%). When compared with the general hospital population, diabetic patients had significantly higher odds of death from vascular disease, renal failure, and infection. Significantly lower odds of death from malignancy and liver disease were observed in patients with diabetes. Of the infections (Table 2), diabetic patients demonstrated higher odds of death from all types of infection except TB and HIV, although only deaths from urosepsis reached statistical significance. Deaths due to HIV infection had a relatively lower prevalence among diabetic patients.

Causes of death were analyzed in age-stratified groups (at a cut-off based on a median age of 56 years), because the mean age differed between cases and controls (Table 3). The higher odds among diabetic deaths due to vascular and renal causes remained significant in both age categories. Differences between diabetic and non-diabetic patients in mortality due to infection disappeared in the < 56 years group

Table 1 Primary causes of death in diabetic (case) and non-diabetic (control) patients

Cause of death	Cases *n* = 315 (%)	Controls *n* = 307 (%)	OR (95% CI)	*P*-value
Vascular disease	121 (38.4)	41 (13.3)	4.05 (2.67–6.16)	<0.0001
Infection	108 (34.3)	75 (24.4)	1.61 (1.12–2.32)	0.007
Renal	28 (8.9)	4 (1.3)	7.39 (2.53–29.27)	<0.001
Malignancy	28 (8.9)	97 (31.6)	0.21 (0.13–0.34)	<0.0001
Respiratory	8 (2.5)	15 (4.9)	0.51 (0.19–1.29)	0.121
Liver	6 (1.9)	24 (7.8)	0.23 (0.08–0.59)	0.0006
Road traffic accidents	4 (1.3)	9 (2.9)	0.43 (0.09–1.55)	0.147
Others*	12 (3.8)	42 (13.8)	0.25 (0.12–0.50)	<0.0001

Unless indicated otherwise, data show the number of patients in each group, with percentages given in parentheses.
*''Others'' includes deaths due to gastrointestinal, hematological, dermatological, burns, congenital heart disease, connective tissue disorders and poisonings.
OR, odds ratio; CI, confidence interval.

Table 2 Infectious causes of death in diabetic (case) and non-diabetic (control) patients

Cause of death	Cases *n* = 108 (%)	Controls *n* = 75 (%)	OR (95% CI)	*P*-value
Urosepsis	21 (19.4)	3 (4.0)	5.79 (1.61–31.29)	0.002
Pneumonia	18 (16.7)	6 (8.0)	2.30 (0.82–7.43)	0.087
TB	15 (13.9)	18 (24.0)	0.51 (0.22–1.19)	0.080
HIV	4 (3.7)	13 (17.3)	0.18 (0.05–0.64)	0.002
Necrotizing fasciitis	6 (5.6)	2 (2.7)	2.15 (0.36–22.25)	0.347
Septicemia	17 (15.7)	13 (17.3)	0.89 (0.38–2.15)	0.775
Diabetic foot	8 (7.4)	0	NA	NA
Others	19 (17.6)	20 (26.7)	0.59 (0.27–1.27)	0.140

Unless indicated otherwise, data show the number of patients in each group, with percentages given in parentheses.
NA, not applicable; TB, tuberculosis; HIV, human immunodeficiency virus; OR, odds ratio; CI, confidence interval.

Table 3 Causes of death in diabetic (case) and non-diabetic (control) patients stratified by age

	<56 years				≥56 years			
	Cases *n* = 96 (%)	Controls *n* = 196 (%)	Adjusted OR	*P*-value	Cases *n* = 219 (%)	Controls *n* = 111 (%)	Adjusted OR	*P*-value
Vascular	32 (33.3)	17 (8.7)	5.26 (2.64–10.48)	<0.0001	89 (40.6)	24 (21.6)	2.48 (1.45–4.24)	<0.0001
Infection	29 (30.2)	58 (29.6)	1.01 (0.60–1.75)	0.91	79 (36.1)	15 (13.5)	3.61 (1.92–2.75)	0.001
Renal	15 (15.6)	2 (1.0)	17.96 (3.73–86.29)	<0.0001	13 (5.9)	3 (2.7)	2.27 (0.63–8.18)	0.19
Malignancy	11 (11.5)	58 (29.6)	0.30 (0.15–0.62)	0.0006	17 (7.8)	39 (35.1)	0.15 (0.07–0.30)	<0.0001
Respiratory	2 (2.1)	1 (0.5)	4.14 (0.36–46.83)	0.21	6 (2.7)	14 (12.6)	0.19 (0.07–0.53)	0.0004
Liver	2 (2.1)	20 (10.2)	0.18 (0.04–0.83)	0.01	4 (1.8)	4 (3.6)	0.49 (0.12–2.03)	0.32
RTA	2 (2.1)	8 (4.1)	0.50 (0.10–2.40)	0.38	2 (0.9)	2 (1.8)	0.50 (0.06–3.63)	0.48
Other*	3 (3.1)	32 (16.3)	0.16 (0.04–0.57)	0.001	9 (4.1)	10 (9.0)	0.43 (0.05–0.57)	0.07

Unless indicated otherwise, data show the number of patients in each group, with percentages given in parentheses.
*''Others'' includes deaths due to gastrointestinal, hematological, dermatological, burns, congenital heart disease, connective tissue disorders and poisonings.
RTA, road traffic accident; OR, odds ratio; CI, confidence interval.

but persisted in the ≥56 years group. Younger diabetic patients (< 56 years) showed lower odds of death due to liver disease, whereas older diabetic patients (≥56 years) had lower odds of death from respiratory disease. Malignancy-related deaths were significantly lower in both age groups.

Table 4 Causes of death in diabetic (case) and non-diabetic (control) patients stratified by gender

	Male				Female			
	Cases n = 207 (%)	Controls n = 189 (%)	OR (95% CI)	P-value	Cases n = 108 (%)	Controls n = 118 (%)	OR (95% CI)	P-value
Vascular	87 (42.1)	27 (14.2)	4.35 (2.59–7.34)	<0.0001	34 (31.5)	14 (11.9)	3.41 (1.63–7.22)	0.0001
Cardiovascular	62 (30)	17 (9)	4.33 (2.34–8.07)	<0.0001	27 (25)	11 (9.3)	3.24 (1.44–7.43)	0.002
Cerebrovascular	25 (12.1)	10 (5.3)	2.46 (10.9–5.66)	0.028	7 (6.5)	3 (2.5)	2.66 (0.60–13.35)	0.265
Infection	67 (32.4)	48 (25.3)	1.41 (0.89–2.23)	0.157	41 (38)	27 (22.9)	2.06 (1.11–3.84)	0.020
Urosepsis	12 (5.8)	0 (0.0)	NA	NA	8 (7.4)	3 (2.5)	3.07 (0.71–15.03)	0.165
Pneumonia	9 (4.3)	3 (1.6)	2.82 (0.69–13.34)	0.191	9 (8.3)	3 (2.5)	3.48 (0.83–16.74)	0.101
TB	11 (5.3)	12 (6.3)	0.83 (0.33–2.070	0.822	4 (3.7)	6 (5.3)	0.72 (0.16–2.98)	0.857
HIV	4 (1.9)	9 (4.8)	0.39 (0.10–1.43)	0.195	0 (0.0)	4 (3.4)	NA	NA
Necrotizing fasciitis	4 (1.9)	1 (0.5)	3.70 (0.39–87.81)	0.424	2 (1.9)	1 (0.8)	2.19 (0.15–61.82)	0.945
Septicemia	10 (4.8)	6 (3.2)	1.55 (0.51–4.90)	0.561	8 (7.4)	7 (5.9)	1.27 (0.40–4.06)	0.859
Diabetic foot	6 (2.9)	NA	NA	NA	2 (1.9)	NA	NA	NA
Other infections	12 (5.8)	17 (9.0)	0.62 (0.27–1.42)	0.304	7 (6.5)	3 (2.5)	2.66 (0.60–13.35)	0.265
Renal	18 (8.7)	4 (2.1)	4.40 (1.37–15.70)	0.008	10 (9.1)	1 (0.8)	11.49 (1.53–253.61)	0.008
Malignancy	16 (7.7)	57 (30.1)	0.19 (0.10–0.36)	<0.0001	11 (10.1)	39 (33.1)	0.23 (0.10–0.50)	<0.0001
Respiratory	5 (2.4)	9 (4.7)	0.50 (0.14–1.65)	0.321	3 (2.8)	8 (6.8)	0.39 (0.08–1.69)	0.276
Liver	3 (1.4)	21 (11)	0.12 (0.03–0.42)	0.0001	3 (2.8)	3 (2.5)	1.10 (0.17–6.97)	0.760
RTA	4 (1.9)	7 (3.6)	0.51 (0.12–1.99)	0.444	0 (0.0)	2 (1.7)	NA	NA
Hyperosmolar coma	1 (0.5)	NA	NA	NA	0 (0.0)	NA	NA	NA
DKA	0 (0.0)	NA	NA	NA	3 (2.8)	NA	NA	NA
Others*	6 (2.9)	16 (9)	0.32 (0.11–0.90)	0.028	3 (2.8)	24 (20.3)	0.11 (0.03–0.41)	0.0001

Unless indicated otherwise, data show the number of patients in each group, with percentages given in parentheses.
*''Others'' includes deaths due to gastrointestinal, hematological, dermatological, burns, congenital heart disease, connective tissue disorders and poisonings.
NA, not applicable; DKA, diabetic ketoacidosis; RTA, road traffic accident; TB, tuberculosis; HIV, human immunodeficiency virus; OR, odds ratio; CI, confidence interval.

The causes of mortality stratified by gender are shown in Table 4. Deaths due to cardiovascular and cerebrovascular disease were higher in diabetic men. A similar trend was observed for cardiovascular disease among women. An increased risk of death due to infections was more commonly seen in female diabetic patients. Although renal deaths were significantly higher among diabetics, no gender differences were observed.

HbA1c data during final hospitalization were available for 122 cases. Of these, 25.4% of deaths were associated with very poor glycemic control (HbA_{1c} > 10%), whereas 40.2% of deaths occurred among subjects whose HbA_{1c} was >7–10%, and 34.4% of deaths were in well-controlled patients with an HbA_{1c} of ≤7%. The clinical characteristics did not differ from the diabetic deaths where HbA1c data were not available (data not shown).

Discussion

The present study focuses on the causes of mortality among diabetic inpatients in a tertiary referral center in south India. Our results make an important contribution towards characterizing the diabetes epidemic in India.

In our hospital population, patients with diabetes listed on their death certificate died at nearly twice the rate of non-diabetic hospital inpatients. The major cause of death among patients with diabetes was vascular disease (38.5%), followed by infections (34.3%) and renal disease (8.9%); all of these parameters reached statistical significance when compared with non-diabetic patients. This demonstrates a changing trend from infections to vascular deaths among diabetics in India.

In 1999, Zargar et al.[18], using a multiple cause of mortality analysis, reported infection (33.8%) as the major cause of death in diabetics, followed by coronary heart disease (16.3%) and cerebrovascular disease (13.7%). When they updated their data in 2009, infections remained as the leading cause (40.9%), followed by chronic renal failure (33.6%), cardiovascular disease (16.9%), and cerebrovascular disease (13.2%).[17] Looking at the primary cause of death in 2002, Bhansali et al.[16] also reported infections (46.5%) as the major

cause of death, followed by coronary artery disease (17.4%), chronic renal failure (9.7%), and cerebrovascular disease (6.0%). One population-based study from south India in recent years did report vascular disease as the leading cause of death among diabetics (52.9%), with infections representing only 5.9% of deaths.[19] The unavailability of regular autopsy data in India means that authors had to rely on reports and verbal communications from non-medical personnel (family members, police officers) to determine the cause of death in many cases, which cautions comparisons with medically verified deaths. Therefore, our study represents the first hospital-based study in recent years to report vascular disease as the leading cause of death in diabetic patients and provides evidence that chronic hyperglycemia, in addition to impaired β-cell function and reduced insulin sensitivity, contributes to endothelial dysfunction and increased cardiovascular morbidity and mortality in diabetics. However, the present study cannot rule out the possibility that the differences observed may be due to variabilities in mortality-reporting patterns between different institutions in India. It is also possible that the reduced infection-related deaths in our setting are due to local hospital policies, such as high-quality routine surveillance by the hospital's Microbiology department and the aggressive treatment of infections.

Age-stratified analyses showed that death due to infections was more common in older diabetics >56 years of age. This result is likely to be due to the fact that HIV was almost entirely a disease of the younger age group and was a less common cause of death among diabetics in the present study. The reasons for the diminished HIV-related deaths among diabetics in our population is unclear, although a worsening metabolic profile and increased impaired glucose tolerance and diabetic risk have been shown to be associated with long-term antiretroviral therapy.[20] This may represent the underreporting of diabetes on the death certificates of patients dying of HIV, in contrast with other infectious diseases. It also appears paradoxical that deaths due to HIV infection were more common in the younger age groups among non-diabetic individuals, even within the age-stratified subgroups (data not shown), and this may represent a selection bias. Studies matched for age could clarify this question.

Some demographic trends in our population warrant explanation. First, the mean age of death in diabetic and non-diabetic patients in our population was 60.5 and 50.2 years, respectively, and these figures were comparable to those of previous reports from India wherein deaths were reported in men and women at a mean age of 69.07 and 57.36, respectively.[17] Diabetes appears to disproportionately affect older patients, resulting in a relatively older average age for diabetic deaths. It also remains important to note that, in India, a number of elderly patients die at home rather than in hospital, leading to a relatively younger mean age of death in the hospital-based setting. Zargar et al. [18] previously reported that one-sixth of all diabetic deaths occurred in people aged <50 years in a tertiary care center in north India.

Second, our data point to certain gender discrepancies in diabetes outcomes in India. Mortality rates between men and women do not appear to differ when total hospital admissions are considered. However, diabetic men are admitted to our hospital (CMC) twice as frequently as women with diabetes, even though population-based screening studies in India have reported equal rates of diabetes among men and women.[21,22] Moreover, men in our hospital with diabetes die at an older age than women (61.9 vs 58.0 years), despite having a lower average life expectancy according to data generated by the Indian National Census (63.9 years in men vs 66.9 years in women; http://www.who.int/countries/ind/en/, accessed 8 November 2011). It is possible that women with diabetes are less likely to seek hospitalization in India. However, one should be cautious in extrapolating the impact of hospital-based data to the general population. Proper characterization of these differences requires a more comprehensive analysis of population mortality data.

The present study has several limitations. First, death certificate-based studies have established problems in terms of the underreporting of diabetes.[23,24] This is a limitation that our study shares with other studies using a similar methodology. Further research is required to clarify patterns of reporting relative to the actual causes of death in the Indian context. Second, in India, the annual registration of deaths constitutes only approximately one-third of the total number of deaths that occur, with the remaining 66% occurring at home without registration, leading to a paucity of information with regards to overall causes of death nationwide.[25] Our data are from a tertiary care center and therefore represent a select group of diabetic patients, making it difficult to extend the findings to the general population. Finally, HbA1c levels were not available for 193 of the 315 subjects, preventing us from being able to adequately assess the contribution of glycemic status to mortality in our population. We also acknowledge that there could be a minor degree of selection bias among controls,

although systematic random sampling was used for their recruitment.

In conclusion, we report that vascular disease is the leading cause of death among diabetics in our hospital-based study from southern India. Although good glycemic control and the appropriate treatment of infections remain important goals for diabetes care in India, our data suggest that increased attention should be given to addressing vascular risk factors by appropriate management of cholesterol levels and blood pressure at all levels of health care as we seek to prevent excessive diabetic deaths in India.

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Disclosure

None declared.

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