

Regional variation in diabetic retinopathy and associated factors in Spectrum of Eye Disease in Diabetes (SPEED) study in India—Report 5

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Purpose: To study the zonal variations in diabetic retinopathy (DR) and associated factors in people with known type 2 diabetes mellitus (T2DM) attending large eye care facilities in different regions of India. **Methods:** In this cross-sectional eye-care facility-based study, India was divided into five zones; large eye care facilities with a good referral base and offering an entire range of care for patients with DR were invited. First-time T2DM attendees aged ≥ 18 years were recruited. All subjects received a comprehensive systemic and ophthalmic examination. DR and systemic diseases were classified as per the international/national standards. Findings were compared between the zones and with the national average. **Results:** Fourteen eye-care facilities (15% public) from five zones participated. In the cohort of 11,173 people, there were more males (59%); the average age was above 45 years, and in 57%, DM had been diagnosed more than 5 years earlier. Compared with the overall study population, the proportion of people with any DR, sight-threatening DR, and blind were higher in the east zone (42.5%, 95% confidence interval [CI]: 40.2–44.8; 24.3%, 95% CI 22.3–26.3, and 11.5%, respectively); diabetic macular edema was more frequent in the south zone (12.2%, 95% CI 11.2–13.2); people with moderate-to-severe visual impairment were more in the west zone (32.1%) and higher proportion of people in the south-central zone had systemic hypertension (56.8%, 95% CI 54.8–58.9). **Conclusion:** The zonal variation in DR and related vision loss could be related to variable health-seeking behavior, availability, and confidence in the available services.

Key words: Diabetic macular edema, diabetic retinopathy, India, sight-threatening diabetic retinopathy

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The SPEED (Spectrum of Eye Disease in Diabetes), a multicenter, cross-sectional, observational clinic-based study, was designed to collect data from major eye-care facilities in India to identify the spectrum of eye disorders in people with known type-2 diabetes mellitus (T2DM). Fourteen large tertiary eye-care hospitals (2 public and 12 private, including 1 diabetes specialty facility) across the country participated in the study between August 2016 and January 2017. These 14 hospitals were located in 5 zones—north, east, west, south, and south-central in 11 cities in India. The study recruited 11,182 people living with T2DM.

The published data of SPEED include eye disorders in people with diabetes, the comorbidities, presence of diabetic retinopathy (DR), sight-threatening diabetic retinopathy (STDR), retinal vascular occlusion, and glaucoma.^[1-4] These reports showed that the age-standardized proportion of DR in people with T2DM was 32.3% (95% confidence interval [CI]: 31.4–33.2), and hypertension (48.2%; 95% CI, 47.5–49.4) was the most common systemic comorbidity.^[1] On multivariate

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analysis, a statistically significant association for increased risk of DR were male gender (odds ratio [OR] 1.57; 95% CI, 1.16–2.15), elevated glycated hemoglobin (HbA1c >10%; OR 2.39; 95% CI, 1.15–5.22), history of hypertension (OR 1.42; 95% CI, 1.06–1.88), and duration of diabetes longer than 15 years (OR 5.25; 95% CI, 3.01–9.15).^[2] Retinal vein occlusion (two-thirds with branch retinal vein occlusion) was detected in 3.4% of people,^[3] and glaucoma was diagnosed in 4.9% (three-quarters with bilateral and open-angle) in this cohort.^[4]

Zonal variation of DM has been reported from India (in 2016, DM was highest in the southern states of Kerala and Tamil Nadu; least in eastern states).^[5,6] But there are no reports on similar zonal variation of DR. In this report, we reanalyzed the SPEED data per five zones of the country to identify any demography differences, comorbidity, and clinical presentations.

Methods

Details of the SPEED methodology have already been published.^[1] In brief, the study included all new patients with T2DM attending the retina clinics of 14 participating eye care facilities. These centers were selected because of their large patient volume and referral base, comprehensive eye care facility, and the expertise and ability to treat all types of DR and its sequelae. The six zones of India^[7] were reconfigured into five zones—north, south, east, west, and south-central, by combining the northeast states and the east zone as one entity; the two southern states (Andhra Pradesh and Telangana) were combined with the central zone (and renamed southcentral zone).

All centers had obtained approval from their ethics committees, and all adhered to the tenets of the Declaration of Helsinki for research involving human subjects. The health

personnel in each eye care facility collected the data using a standard format. All data were stored in a shared repository at the Indian Institute of Public Health (IIPH, Public Health Foundation of India), Hyderabad, India.

We defined a person as diabetic when the current plasma glucose level was >126 mg/dL, or 2-h post-load glucose was >200 mg/dL, or random plasma glucose was >200 mg/dL, or the HbA1c was >6.5%. We defined good control of DM when the current plasma glucose level was as follows: fasting: <110 mg/dL, 2-h post-load glucose <140 mg/dL, or HbA1c <5.7%.^[8] Hypertension was defined as per the Indian norms specified by the National Health Mission, as a systolic blood pressure of >140 mmHg and diastolic blood pressure of >90 mmHg.^[9] Cardiovascular disease (chiefly coronary artery disease) was defined using the World Health Organization definition,^[10] and diabetic kidney disease and neuropathy in people with diabetes was defined using the National Institute of Diabetes and Digestive and Kidney Disease (NIDDK, NIH, USA) definitions.^[11]

Distance presenting vision impairment (VI) was classified using the National Program for Control of Blindness and Visual Impairment (Government of India) categories defined as follows: near-normal vision: $\geq 6/9$; early VI: 6/12–6/18; moderate VI: <6/18–6/60; severe VI: <6/60–3/60; blind <3/60.^[12] The International Classification of Diabetic Retinopathy was used to classify and grade the presence and severity of DR.^[13] We enquired about six systemic comorbidities among individuals with diabetes mellitus. These were hypertension, cardiovascular disease (CVD), stroke, diabetic kidney disease (DKD), neuropathy, and limb amputation due to diabetes.

The collected data included demography, the type and duration of DM, and all ocular conditions documented after a comprehensive examination of each eye. Only eyes where

Table 1: Sociodemographic characteristics of respondents

Zone	People	Gender, n (%) (mean and SD age)		DM duration n=11,180 (99.9%)	
		Female	Male	≤ 5 years n (%) 95% CI	> 5 years* n (%) 95% CI
South	4368	1871 (42.8) (59.2 ±)	2497 (57.2) (58.410.6)	1878 (43.1) (41.6–44.6)	2488 (56.9) (55.4–58.4)
S. central	2324	891 (38.3) (58.5)	1433 (61.7) (59.010.7)	952 (41.0) (39.0–43.0)	1372 (59.0) (57.0–61.0)
West	984	369 (37.5) (56.9)	615 (62.5) (59.1)	570 (57.9) (54.8–61.0)	414 (42.1) (39.0–45.2)
North	1706	808 (47.4) (54.9)	898 (52.4) (56.0)	788 (46.2) (43.8–48.6)	918 (53.8) (51.4–56.2)
East	1800	623 (34.6) (57.1)	1177 (65.4) (59.0)	539 (29.9) (27.8–32.1)	1261 (70.1) (67.9–72.2)
All zones	11,182	4562 (40.8) (58.4)	6620 (59.2) (57.8)	4727 (42.3) (41.4–43.2)	6453 (57.7) (56.8–58.6)

*Chi square: 224.4, $P < 0.001$

Table 2: Categorized vision among respondents in different zones

Zone (n)	Normal n (%)	Early n (%)	MSVI n (%)	P	Blind n (%)	P	Uncertain/Variable n (%)
South (4368)	2462 (56.3)	793 (18.1)	926 (21.2)	0.261	186 (4.3)	0.374	1 (0.02)
South central (2324)	1145 (49.3)	421 (18.1)	597 (25.7)	0.161	97 (4.2)	0.477	64 (2.7)
West (984)	380 (38.6)	221 (22.5)	316 (32.1)	<0.001*	67 (6.8)	0.794	0
North (1706)	998 (58.5)	246 (14.4)	337 (19.7)	0.173	110 (6.5)	0.839	15 (0.9)
East (1800)	957 (53.2)	225 (12.5)	404 (22.4)	0.790	208 (11.5)	0.007*	6 (0.3)
All zones (11,182)	5942 (53.1)	1906 (17.1)	2580 (23.0)	-	668 (6.0)	-	86 (0.8)

*Significant; MSVI: Moderate-to-severe visual impairment; VI: Visual impairment

the fundus could be examined by indirect ophthalmoscopy or photographed with a retinal camera were included to estimate and classify retinal vascular disease, including DR. The following data were analyzed by zone: demographic data, systemic comorbidities, and ophthalmic disorders.

Statistical analysis

Stata 14SE for Window (Stata Corp, TX USA) was used for statistical analysis. Data were cross-tabulated, and means and standard deviations for continuous variables and percentages for categorical variables were compiled. Chi-square was performed to look for the association between zones and other variables such as blindness, hypertension, CVD, any DR, and STDR in each zone were compared with the averages of this cohort and between the zones. For all statistical tests, a *P* value <0.05 was considered statistically significant.

Results

Demography

The 14 study locations included two large public health facilities, 1 tertiary diabetes care facility with integrated diabetic eye care, and 10 non-government not-for-profit eye care facilities. These eye care facilities were located in 11 cities—3 in North India (Chandigarh—1; Delhi—2), 2 in South Central India (both in Hyderabad), 4 in South India (Angamaly, Kerala—1; Chennai—2; Madurai, Tamil Nadu—1), 2 in West India (1 each in Pune, Maharashtra, and Surat, Gujarat), and 3 in East India (1 each in Bhubaneswar, Odisha; Purba Medinipur, Bengal; and Guwahati, Assam).

The study recruited 11,182 people with T2DM; all of them lived in the zone of India under consideration; the lowest recruitment was from the west zone, and 59% were male and 41% female. The proportion of females was lower than the national average in three zones—south-central, east, and west. The average age was 58.2 years (± 10.6 years; range 39–96 years) [Table 1]. Data on the duration of DM were elicited from 11,180 (99.9%) people. Patients living in the east zone were more likely to have had diabetes for more than 5 years (70.1%), which was higher than the cohort average (57.7%), and the difference in duration of DM between zones was statistically significant.

In the study, 82% ($n=9169$) people were on oral hypoglycemic agents (highest in north zone: 88.5%; lowest in east zone: 67.7%) and 7.7% ($n = 865$) people were on insulin alone (highest in east zone: 17%; lowest in north zone: 2.5%). Diabetes were controlled according to the definition of the study in 32.1% people (highest in the south-central zone: 56.8%; lowest in the north zone: 7.9%).

On presentation, 6.0% ($n = 668$) participants were blind, and 23% had moderate-to-severe visual impairment (MSVI; $n = 2580$) in this cohort. The highest proportion of blind people was in the east zone (11.5%), and the highest proportion of people with MSVI on presentation was in the west zone (32.1%) [Table 2]. The visual acuity measurement was either variable/uncertain in patients who had presented with an acute red eye (0.8%).

Systemic comorbidities

The most common self-reported systemic comorbidity in this cohort of patients was hypertension (48.4%; $n = 5416$),

Table 3: Systemic comorbidities in people with type 2 diabetes mellitus

Zone	HTN (1)		CVD (2)		Stroke (3)		Neuropathy (4)		DKD (5)	
	Yes n (%), 95% CI	No (%)	Yes n (%), 95% CI	No (%)	Yes n (%), 95% CI	No (%)	Yes n (%), 95% CI	No (%)	Yes n (%), 95% CI	No (%)
South	1997 (45.7; 44.2-47.2)	2371 (54.3)	374 (8.6; 7.7-9.4)	3994 (91.4)	31 (0.7; 0.4-1.0)	4337 (99.3)	50 (1.1; 0.9-1.5)	4318 (98.9)	88 (2.0; 1.6-2.5)	4280 (98.0)
S. central	1321 (56.8; 54.8-58.9)	1003 (43.2)	70 (3.0; 2.4-3.8)	2254 (97.0)	8 (0.3; 0.1-0.7)	2316 (99.7)	3 (0.1; 0.03-0.4)	2321 (99.9)	32 (1.4; 0.9-1.9)	2292 (98.6)
West	274 (27.8; 25.1-30.8)	710 (72.1)	19 (1.9; 1.2-3.0)	965 (98.1)	1 (0.1; 0.03-0.6)	983 (99.9)	0	984 (100)	1 (0.1; 0.03-0.6)	983 (99.9)
North	811 (47.5; 45.1-50.0)	895 (52.5)	115 (6.7; 5.6-8.0)	1591 (93.3)	4 (0.2; 0.06-0.6)	1702 (99.8)	11 (0.6; 0.3-1.2)	1695 (99.4)	17 (1.0; 0.6-1.6)	1689 (99.0)
East	1013 (56.3; 53.9-58.6)	787 (43.7)	75 (4.2; 3.3-5.2)	1725 (95.8)	5 (0.3; 0.09-0.6)	1795 (99.7)	21 (1.2; 0.7-1.8)	1779 (98.8)	16 (0.9; 0.5-1.4)	1784 (99.1)
All zones	5416 (48.4; 47.5-49.4)	5766 (51.6)	653 (5.8; 5.4-6.3)	10,529 (94.2)	49 (0.4; 0.32-0.6)	11,133 (99.6)	85 (0.8; 0.6-0.9)	11,097 (99.2)	154 (1.4; 1.2-1.6)	11,028 (98.6)

(1) Chi square 290.6, $P<0.001$; (2) Chi square 131.7, $P<0.001$; (3) Chi square 13.1, $P=0.011$; (4) Chi square 32.61, $P<0.001$; (5) Chi square 23.84, $P<0.001$

Table 4: Diabetic retinopathy status

Zone	Any DR (1)		DME (2)		STDR (3)	
	Yes n (%) (95% CI)	No n (%) (95% CI)	Yes n (%) (95% CI)	No n (%) (95% CI)	Yes n (%) (95% CI)	No n (%) (95% CI)
South	1362 (31.2) (29.8-32.6)	3006 (68.8) (67.4-70.2)	533 (12.2) (11.2-13.2)	3835 (87.8) (86.8-88.8)	846 (19.4) (18.2-20.6)	3522 (80.6) (79.4-81.8)
South central	716 (30.8) (28.9-32.7)	1608 (69.2) (67.3-71.1)	44 (1.9) (1.4-2.5)	2280 (98.1) (97.5-98.6)	358 (15.4) (14.0-16.9)	1966 (84.6) (83.1-86.0)
West	250 (25.4) (22.7-28.2)	734 (74.6) (71.8-77.3)	73 (7.4) (5.9-9.2)	911 (92.6) (90.8-94.1)	129 (13.1) (11.1-15.4)	855 (86.9) (84.6-88.9)
North	518 (30.4) (28.2-32.6)	1188 (69.6) (67.4-71.8)	191 (11.2) (9.7-12.8)	1515 (88.8) (87.2-90.3)	363 (21.3) (19.4-23.3)	1343 (78.2) (76.7-80.6)
East	765 (42.5) (40.2-44.8)	1035 (57.5) (55.2-59.8)	172 (9.6) (8.2-11.0)	1628 (90.4) (89.0-91.8)	437 (24.3) (22.3-26.3)	1363 (75.2) (73.6-77.7)
All zones	3611 (32.3) (31.4-33.2)	7571 (67.7) (66.8-68.6)	1013 (9.1) (8.5-9.6)	10169 (90.9) (90.4-91.5)	2133 (19.1) (18.4-19.8)	9049 (80.9) (80.2-81.6)

(1) Chi square 114.83, $P < 0.001$; (2) Chi square 210.44, $P < 0.001$; (3) Chi square 80.13, $P < 0.001$. *Significant. DME: Diabetic macular edema; DR: diabetic retinopathy; STDR: sight-threatening retinopathy

and the least common was stroke (0.4%; $n = 49$). The highest proportions with these comorbidities by zone were as follows: hypertension (south-central zone: 56.8% and east zone 56.3%), cardiovascular disease (south zone: 8.5%), stroke (south zone: 0.7%), diabetic kidney disease (south zone: 2.0%), limb amputation (north and south zone 0.1% each), and neuropathy (south zone: 1.1%). Differences between zones were statistically significant for hypertension, cardiovascular disease, stroke, and diabetic kidney disease [Table 3].

Diabetic retinopathy

We report DR in three categories: any DR, diabetic macula edema (DME), and STDR. In this cohort, 32.3% of people with DM had any DR (highest in the east zone 42.5%); 9.1% had DME (high in south zone 12.2%), and 19.1% people had STDR (highest in the east zone, 24.3%) [Table 4]. For each type of DR, differences between zones were statistically significant.

Discussion

Diabetes mellitus

The prevalence of DM in India was 5.5% in 1990 and 7.7% in 2016.^[6] But it is not uniformly distributed between the states (India has 28 states and 8 union territories) and inside the states. The prevalence of DM in people in urban areas is nearly two times of people in the rural area (urban: 11.2%; rural: 5.2%).^[5] There was a higher prevalence of DM in a few southern states (Kerala, Tamil Nadu, and Karnataka) and few northern states (Punjab, Delhi) in 1990 and 2016.^[6] Lower prevalence of DM was reported from the east and far-east states of India. But it was also noted that significantly greater changes in prevalence from 1990 to 2016 occurred in the states that had a lower prevalence of DM, such as the central, east, and far eastern states of India.^[6] In this cohort, there were proportionately a greater number of people in the east zone with DM of longer than 5-year duration (70.1%).

Diabetic retinopathy

The prevalence and severity of DR that usually develops 5–7 years after the onset of T2DM, and around puberty in T1DM, depend on many factors, such as the study location (rural vs. urban; high-income vs. low-income country), the study type (population vs. clinic-based), and the study period. The reports of the proportion of people with DR in people with DM in India in the last two decades range from 10.3% to 18.2% in rural areas^[14-16] and from 14.5% to 26.8% in urban areas.^[17-20] In the SPEED study, 32.3% of people with T2DM attending the eye care facilities had any retinopathy.^[2] The higher proportion of DR reported in the present study is because it was a tertiary hospital-based study, which is also referral institutions, and therefore people needing treatment would be utilizing these services. Also, these centers were all urban centers, and it is possible that more people from urban than rural areas attended the eye care facilities.

DR is likely to increase as the prevalence of diabetes is increasing globally and in India. It is estimated that approximately one-third of people with T2DM develop DR in 5–7 years after the diagnosis.^[21] The 2016 report indicated a higher prevalence of DM in certain southern and northern Indian states, but bigger shifts in DM prevalence occurred in the central, east, and northeast states.^[6] However, the proportion of people with DR in the current SPEED study conducted at the

nearly similar period, 2016–2017, did not appear necessarily to be at par with the regional prevalence of DM in India; it probably reflected the shifting trend of DM prevalence in India.

Zonal variation of DR

The current data showed that the east zone (in this study, eye care facilities from Odisha, Bengal, and Assam states) reported a higher proportion in any DR and STDR, the south zone (in this study Tamil Nadu and Kerala states) reported a higher proportion of DME, and north zone (in this study Chandigarh and Delhi union territories) in DME and STDR compared to other zones. Also, in the east zone, there was more number of people with diabetes longer than 5 years (70.1% vs. this cohort average of 57.7%), a higher proportion of people were blind (11.5% vs. this cohort average of 6.0%), a higher proportion of people had associated hypertension (56.3% vs. this cohort average of 48.4%). With a higher proportion of people with diabetes living in the south and north zone of India,^[6] one could probably expect a higher disease burden.

One should expect a lesser disease burden in India's east zone with a lower prevalence of DM. But our analysis showed a larger proportion of people were affected in the east zone compared to other zones, both in any DR and STDR. The visual impairment in people with DR depends on the time and efficacy of treatment. In the current analysis, a higher proportion of people with DR in the east zone were blind.

One could attribute these findings to three hypotheses: (1) the larger age-standardized percentage change of diabetes prevalence between 1990 and 2016^[6]; (2), the health-seeking behavior of the people in this region could be different; and (3), the health system, particularly for the care of non-communicable diseases, and specifically diabetes, could be less advanced/poorly used in the region. In the national health ranking in 2019, three study states of the east zones (Bengal, Assam, and Odisha) ranked below, at 11, 15, and 19, respectively, among India's 21 large states.^[22]

Comparison with the latest national survey in India

The country-wide population-based survey, 2015–2019 using the Rapid Assessment of Avoidable Blindness 6 (RAAB 6), examined 577,776 (42.6% male) people aged 50 years or older.^[23] The survey showed that 11.8% people had DM (8.0% known and 3.8% new). Amongst the people with DM, 16.9% people had any DR, 7.0% people had DME, and 3.6% people had STDR. Besides, 2.1% people were blind and 13.7% had visual impairment. This survey included three districts in East India (survey was done in 21 districts), one in Odisha and two in West Bengal. In these three districts, the prevalence of any DR and STDR was 17.3–20.4% and STDR was 2.0–4.2%, respectively. All these figures were lower than in the reported cohort for two reasons: (1) more visually impaired people will report to a clinic and (2), the RAAB study did not examine people under 50 years old.

India program planning for NCD care

In response to the increased burden of non-communicable diseases, the Government of India has created the National Program for Prevention and Control of Cancer, Diabetes, Cardiovascular Disease, and Stroke (NPCDCS) in 2010, with a budget allocation of INR 60.00 billion in the 12th 5-year

plan (2012–2017). The objectives of NPCDCS are to prevent NCDs through advocacy (behavioral and lifestyle changes), screening (early diagnosis), capacity building (infrastructure development and health personnel training), and periodic evaluation (surveillance and monitoring). By March 2016, the Government of India had established NCD cells and NCD clinics in 298 and 293 districts, respectively, of 718 districts in India.^[24] In 2016, this was further expanded to a “National Multisectoral Action Plan” (NMAP) for Prevention and Control of Common Non-Communicable Diseases (2017–2022) with the engagement of 34 ministries, the private sector, and civil society. The NMAP has 10 targets and indicators for 2020 and 2025; the ones closely related to DM (and DR) are reduction of obesity in general, increased physical activity (targets 2020: 5%; 2025: 10%), reduction in blood pressure (targets 2020: 10%; 2025: 25%), and availability of affordable medicine (targets 2020: 60%; 2025: 80%).^[25]

Early diagnosis and referral

It is also understood that putting together a program and providing facilities alone cannot bring about the desired results unless there is a concurrent change in people's behavior and the community and trust in the health system. DR is a slowly progressing disease. Hence, screening people with or at risk of developing DM and appropriate referral is crucial in the management.^[26] Studies in India and elsewhere have demonstrated that medical facilities closer to the residence and disease detection combined with definitive treatment, such as laser in the appropriate stage of retinopathy, increased compliance.^[27,28]

Goal—Universal Health Coverage

Good knowledge of the disease is usually associated with a positive attitude and good practice.^[29] A study in East India (Bhubaneswar) has shown that KAP (knowledge-attitude-practice) is generally poor in an average educated individual.^[30] Thus, a more in-depth inquiry is necessary to understand the poor health-seeking behavior of people with DM in East India. A robust health system directed explicitly to care of diabetes is required in this region to reduce the blindness, and visual impairment secondary to DR. Integration of DR screening and management services at the district and subdistrict levels is important so that people can access timely detection and treatment facilities. At the same time, it must be borne in mind that the change in the prevalence of DM between 1990 and 2016 was relatively higher in the eastern India region (Odisha and Bengal) than the South and the South Central zone.^[6] Thus, every effort must be made to meet the targets proposed by NMAP of reducing obesity, reducing hypertension, and increasing physical activity. Concurrently a policy change, in addition to the ones described in NMAP, is required in the digitalization of health information to create a state/national level registry of people with diabetes and related health issues so that targeted efforts could be made to meet the aspiration of universal eye health coverage.^[31] It must be understood that such an upfront investment in screening is likely to improve patient outcomes (and compliance) and would eventually result in downstream programmatic savings.^[32] However, expanding coverage with an increased number of NCD clinics does not necessarily guarantee a benefit unless combined with patient education, motivation, and behavioral change.

Limitations and strengths

This study is not without limitations. The SPEED was a facility-based study, so the findings cannot be generalizable to the population. The spread of patients in each zone was not uniform; neither was it proportionate to the diabetes population. Since all the eye care facilities were in cities or larger towns, most patients recruited into this cohort could be from urban than rural India. Many with early disease may not have reported because of the non-availability of required care, the distance needed to travel, and lack of finance, thus skewing the proportion of people with severe visual impairment or blindness upward.

The strength of the study lies in the fact that it was a large cohort of a patient population with diabetes from all zones of the country, and for the first time, a zonal analysis of DR was done in India.

Conclusion

DR and related blindness were higher in the eastern zone of India than in other zones. These were also proportionately higher than the reported prevalence of diabetes mellitus in the region. This calls for greater advocacy to improve the knowledge-attitude-practice of people with diabetes at one end and qualitative/quantitative increase in the service provision as per India's national program. A population-based study would provide more precise data that would help in better program planning.

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Conflicts of interest

There are no conflicts of interest.

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