Difference in prevalence of diabetes and diabetic retinopathy among low-altitude dwellers vs. high-altitude dwellers in North India

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Abstract

Background: *Type-2 diabetes mellitus (DM) is one of the leading lifestyle-related chronic disease as its prevalence is expected to rise up to 24.0% in the world by 2025, which was only 6.3% in year 2003.*

Objective: *To understand the high-altitude and low-altitude differentials for DM and diabetic retinopathy (DR) prevalence in a sub-Himalayan state of North India.*

Methods: *The study was carried out in the Shahpur block of Kangra district (altitude 2,404 feet) and the Spiti block of Lahaul and Spiti district (altitude 12,500 feet) of Himachal Pradesh.*

Results: *Among diabetics, the prevalence of DR was observed to be high (18.1%) in low landers and low (5.0%) in high landers. DM was more of a problem among low landers with a prevalence of 12.3% when compared to high landers (7.2%). Overall, the odd ratio of DR was twice as high (2.2; 95% confidence interval [CI]: 1.1-2.3) among patients with an unsatisfactory level of HbA1c (>8.0%) adjusted for gender, age group, smoking status and hypertension.*

Conclusion: *Differential did exist, as DM and DR were significantly lower in high-altitude areas when compared to low-altitude areas.*

Keywords: *diabetes mellitus, diabetic retinopathy, high landers and low landers, retinopathy*

Introduction

Type-2 diabetes mellitus (DM) is one of the leading lifestyle-related chronic diseases as its prevalence is expected to increase up to 24.0% globally by 2025 when compared to 6.3% in the year 2003: most in East Asia and Pacific and least in sub-Saharan Africa region.[1] Worldwide, DM causes estimated 9,59,000 deaths and 19,96,000 disability-adjusted life years.[1] DM-associated mortality and morbidity is due to micro-vascular

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(retinopathy, nephropathy and kidney failure) and macro-vascular (coronary heart disease, stroke, peripheral vascular disease and lower-extremity amputation) complications. Diabetic retinopathy (DR) is one of the serious complications, and if detected late can cause severe and irreversible loss of vision in an affected eye.

Lifestyle factors like physical inactivity, unhealthy diet, tobacco smoking and alcohol consumption are observed to be responsible for the onset of chronic diseases, including DM. Earlier considered only to be the disease of urban, chronic conditions have now been reported from rural areas of the country.[1-4] Evidence from population living in lower-altitude areas are available, but it is scanty for people living in high altitude. Therefore, present study was planned to assess the prevalence of DM and DR among low landers and high landers in a sub-Himalayan state of North India.

Methodology

This study was carried out in Shahpur block (low-altitude belt, 2,404 feet) of Kangra district and Spiti block (high-altitude belt, 12,500 feet) of Lahaul and Spiti district of Himachal Pradesh. This high-altitude belt is also the tribal belt which is a state notified area, and its population resides at an average of 12,500 feet from the mean sea level (MSL), whereas low-altitude areas spread over an average of 2,404 feet from the MSL. Population of tribal area residing in tough environmental conditions, as the area remained isolated from the rest of state due to heavy snowfall for 6 months (November to April), and inter-village connectivity remains disrupted for 3 months (December to February) every year. People living in the tribal area carry out agriculture, horticulture and cattle farming for livelihood. In order to estimate the prevalence of DM, the sample size of 3,445 in each area was calculated assuming 10.0% prevalence, design effect of 4, 80.0% study power and 95.0% level of significance. The villages were considered as the unit (cluster) of the study and 20 clusters with probability proportion to size were selected from the list of villages of each area. Structured interview schedule was administered by the trained field staff along with anthropometry and assessment for DM. It was done in the selected village across its entire households by door-to-door survey among individuals more than 20 years of age. Information on smoking, hypertension, duration of diabetes and family history of DM was collected along with the assessment for fasting blood sugar (FBG) with a standardized glucometer. Individuals with known case of DM and with FBG of ≥126 mg/dl were labelled as diabetics, and all of them were then assessed for glycosylated haemoglobin (HbA1c) with Nyco Card reader. All diabetics were assessed by an ophthalmologist for DR with the Fundus camera (VisuCam-500) along with measurement of intraocular pressure

(IOP) with the use of the tonometer. The informed consent was sought from the participants during the interview, anthropometry, blood sample collection and retinal assessment. The study was funded by the Indian Council of Medical Research, New Delhi, India, and approved by the Institute Ethics Committee. Data was entered and analyzed using the Epi Info software, Centre for Disease Control, Atlanta.

Results

Totally 2,204 individuals in the high-altitude area and 3,404 individuals in the low-altitude area were interviewed and assessed for DM. The prevalence of DM was found to be 7.2% among the high landers and 12.3% among the low landers with the mean FBG level of 101.1 mg/dl and 136.6 mg/dl in the high landers and low landers, respectively. The levels for the mean FBG was 104.9 mg/dl and 158.1 mg/dl in already known cases of DM. The prevalence of DR in the screened population was 0.3% among high landers and 2.2% among low landers. DR was prevalent in 5% and 18.1% of diabetic patients in the high-altitude and low-altitude areas, respectively (Table 1).

Looking for the differential variables, it was observed that the mean age of the screened population was 50.1 years in high landers when compared to 56.3 years in the low landers. The average age of diabetics in high landers was low (51.9 years) when compared to low landers (57.2 years). The age group distribution observed that more than half of the screened and about half of diabetic population were of 20 to 50 years of age in high-altitude area, indicating relatively more representation of younger population.

A gender differential was observed as significantly more proportion of males were screened (41.1% vs. 25.3%) and found diabetic (44.9% vs. 33.2%) in the high-altitude area when compared with the low-altitude area.

The prevalence of known cases of DM among all diabetics was 7.9% among the high landers and 84.4% among the low lander. Among known cases of DM, the regular intake of medicine was reported in 21.7% and 90.3% patients of the high-altitude and low-altitude areas, respectively (Table 1).

Among diabetics who reported history of regular intake of anti-diabetic drugs, the significant difference in the mean level of HbA1c was found to be 9.3 (SD ± 2.5) and 7.7 (SD ± 1.7) (p < 0.0011) among high landers and low landers, respectively. The prevalence of unsatisfactory levels of HbA1c (>8.0%) was observed to be 80.0% among high landers and 40.0% among low landers (p = 0.05) (data not shown). But when assessed for all diabetics (old and new), it was observed that the mean HbA1c was lower among high landers (6.3% vs. 7.7%) with relatively low prevalence for unsatisfactory levels of HbA1c (≥8.0%) among high landers (11.3% vs. 41.1%) when compared to the low landers (Table 2).

Table 1. Distribution of observed variables among screened population and diabetics in high-altitude and low-altitude areas of Himachal Pradesh, India

Variable	Screened population		P-value	Diabetics		P-value
	High landers (2,204)	Low landers (3,404)		High landers (159)	Low landers (418)	
Mean FBS (mg/dl) (±SD)	101.1 (28.3)	136.6 (65.9)	<0.001	104.9 (32.0)	158.1 (51.5)	<.001
Mean age (years) (± SD)	50.1 (10.9)	56.3 (11.3)	<0.001	51.9 (10.0)	57.2 (9.1)	<0.001
Age group (years) (%)						
20-40	26.5	6.9	<0.001	20.2	3.1	<0.001
41-50	35.9	32.3	<0.001	29.1	23.2	0.07
51-60	20.2	28.8	<0.001	30.1	43.7	<0.001
61-70	11.5	21.7	<0.001	16.4	23.4	0.02
>70	5.9	10.2	<0.001	4.1	6.7	0.14
Male (%)	41.1	25.3	<0.001	44.9	33.2	<0.001
Known case of DM (%)				7.9	84.4	<0.001
Family history of DM (%)				2.0	21.2	<0.001
Known case of hypertension (%)				6.5	39.6	<0.001
Taking treatment for DM (%)				21.7	90.3	<0.001
Duration of smoking						

Variable	Screened population		P-value	Diabetics		P-value
	High landers (2,204)	Low landers (3,404)		High landers (159)	Low landers (418)	
<1 year	4.0	2.0	<0.001[a]	2.9	0.0	NA
1-5 year	10.3	7.0	0.13	2.9	2.0	0.01
5-10 year	14.3	2.6	<0.001	20.6	5.9	0.08
>10 year	71.3	95.5	<0.001	73.5	92.2	0.01
Cigarettes per day						
<5	17.8	21.5	0.28	11.8	27.5	0.08
5-10	13.0	19.4	0.04	8.8	13.7	0.73[a]
>10	68.9	58.8	0.01	79.4	58.8	0.04
Ever tested for lipids (%)	0.5	16.6				
Mean blood pressure	127/34	128/78	<0.001	126/88	134/88	<0.001
hypertension stage (mmHg)						
Normal (<120 and <80)	42.8	41.4	<0.001	33.2	39.1	0.13
Pre (120-139 or 80-89)	37.3	39.7	<0.001	19.9	20.3	0.87
Stage-1 (140-159 or 90-99)	12.3	16.9	<0.001	28.4	31.3	0.42
Stage-2 (≥160 or ≥100)	7.6	2.9	<0.001	18.5	9.3	<0.001

[a]Yates' corrected Chi-square

Table 2. Distribution of fasting blood sugar, HbA1c and IOP detected in diabetics and individuals with DR in high-altitude and low-altitude areas of Himachal Pradesh, India

Variable	Diabetics		P-value	Diabetics with DR		P-value
	High landers (159)	Low landers (418)		High landers (8)	Low landers (76)	
Mean FBS (mg/dl) (±SD)	104.9 (32.0)	158.1 (51.5)	<0.001	146.8 (34.4)	185.6 (42.4)	0.12
HbA1C (%) (±SD)	6.3 (1.5)	7.7 (1.7)	<0.001	8.1 (2.0)	8.3 (1.7)	0.82
IOP right (±SD), mmHg	15.8 (4.1)	15.3 (4.3)	0.18	17.8 (4.8)	15.2 (4.1)	0.18
IOP left (±SD), mmHg	15.4 (3.9)	15.5 (4.5)	0.59	17.1 (3.0)	15.7 (4.6)	0.26
High HbA1c (>8.0%)	11.3	41.1	<0.001	66.7	62.2	0.82
Hypertension (Stage-1 and Stage-2) (%)	48.6	40.4	0.95	37.5	47.4	0.85

Among all screened for DM, an assessment for hypertension was performed, finding that the, prevalence of pre-hypertension and stage-1 hypertension was significantly high among low landers, whereas stage-2 hypertension was found to be high among high landers. Among diabetics, a similar but insignificant differential, was observed (Table 1).

Among high landers, the prevalence of smoking was 8.5% when compared to 11.8% among low landers (p < 0.001) with a smoking history for more than 10 years in about 71.3% of high landers and 95.5% of low landers (p < 0.001) (Table 1). Statistical insignificant difference was observed for IOP in both eyes (right: 15.8 vs. 15.3; left: 15.4 vs.15.5) between both areas (Table 1).

As the prevalence of DR was observed to be significantly high among low landers when compared to high landers and the number of DR cases was less in high-altitude area, so a statistically insignificant difference was observed for mean FBS, HbA1c, IOP and individuals with high HbA1c when compared to the low-altitude area (Table 2). Looking for the potential variables for the difference, it was observed that a significant odds ratio (OR) was observed for unsatisfactory

HbA1c levels among diabetics with OR of 19.8 (95% [confidence interval] CI: 3.3-118.2) in high altitude and 2.8 (95% CI: 1.7-4.8) in the low altitude. It was insignificant for gender, age group, smoking and hypertension. The wide CI was observed in high-altitude area because of relatively fewer number of DR cases (8). Therefore, combining all the cases of DR of both areas for assessment we observed that the OR of DR was significantly high among diabetics with high HbA1c, 4.3 (95% CI: 2.6-7.0) and individuals of 61 to 70 years of age, 1.8 (95% CI: 1.1-3.1). Looking for OR across the age group, an insignificant increasing risk from low to high age group was observed. Adjusting for factors like gender, age group, long duration of DM (high HbA1c), smoking and hypertension, it was found that the high HbA1c was associated with DR with an OR of 2.2 (95% CI: 1.2-2.7). It indicates that DR was approximately twice as high among diabetics with long duration of uncontrolled DM (Table 3). All the observed cases of DR were non-proliferative type and not even a single case of proliferative DR was observed in the present study. The most common observation for non-proliferative DR (NPDR) were haemorrhages,

Table 3. Unadjusted and adjusted risk assessment for DR in high-altitude and low-altitude areas of Himachal Pradesh, India

Variable	High landers (8)	Low landers (76)	Both (84)	
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Male	3.8 (0.7-19.2)	1.3 (0.7-2.1)	1.1 (0.7-1.8)	0.9 (0.5-1.6)
Age group in years (%)				
20-40	0.3 (0.0-4.6)	1.3 (0.3-5.0)	0.4 (0.1-1.1)	Constant
41-50	1.4 (0.3-6.3)	0.3 (0.1-0.6)	0.3 (0.1-0.7)	1.6 (0.4-6.6)
51-60	0.7 (0.1-3.8)	1.1 (0.7-1.8)	1.3 (0.8-2.0)	0.7 (0.2-2.6)
61-70	0.7 (0.0-5.9)	1.8 (1.0-3.1)	1.8 (1.1-3.1)	0.3 (0.0-1.3)
>70	3.5 (0.4-31.3)	1.2 (0.5-3.1)	1.6 (0.7-3.8)	0.3 (0.0-1.6)
High HbA1c	19.8 (3.3-118.2)	2.8 (1.7-4.8)	4.3 (2.6-7.0)	2.2 (1.1-2.7)
Smoker	1.2 (0.1-10.1)	1.1 (0.5-2.3)	1.1 (0.6-2.3)	1.0 (0.4-2.3)
Hypertension (Stage-1 & Stage-2)	0.6 (0.1-2.8)	1.4 (0.8-2.3)	1.1 (0.7-1.8)	0.7 (0.4-1.1)

CI: confidence interval; OR: odds ratio

microaneurysms and hard exudates. It was followed with fewer frequent findings of haze, torturous vessels, cotton wool spots and optic disc changes.

Discussion

DR is the most important cause of irreversible loss of vision. India is considered as diabetic capital of the World. Among diabetics, studies observed the prevalence of DR as 18% (CURES)[5] and 19% (APEDS),[6] 10.0%[7] and 21.6%.[8] Current study observed that among diabetics, the prevalence of DR was 18.1% in low-altitude areas and 5% in high-altitude areas. It was of NPDR in nature with significant differential distribution in studied areas. Among screened individuals, it was 2.2% among low landers and 0.3% among high landers. In general population of rural India, the prevalence of DR was observed to be 0.6%, 1.2%, 1.7%, which is quite similar to the present study.[8-10] However, in evidence from rural Bangladesh, DR prevalence was 5.4% in its studied participants.[11] As in the current study, NPDR was the common form in the rural area of Andhra Pradesh (96.4%).[11] DR is dependent on the duration of disease and its treatment, which is an important factor related to DM. The current study observed that the OR of DR was twice as high (2.2; 95% CI: 1.1-2.3) among patients with an unsatisfactory level of HbA1c (>8.0%) adjusted for gender, age group, smoking status and hypertension. As the biological plausibility, the long duration of DM is certainly the risk factor for DR in both the areas.

DM affects people of all ages and races with increasing prevalence worldwide. In certain regions, successive growth and development leads to associated lifestyle changes exemplified by the reduction of physical activity and increased consumption of high-energy processed foods.[12-14] DM prevalence in India ranged from 5.9% to 12.1% (North: 8.6%–11.6%; South: 13.5%–19.5%).[15,16] High prevalence of DM was observed both in urban and rural India (about 2.0%–10.0%),[16] whereas a systematic review for DM in tribal populations of India observed a ranging prevalence from 0.7% to 10.0%, with a final estimate of 5.9%.[17] The present study tends to understand the pattern of DM and DR as its complication among low landers and high landers. In the high-altitude area with limited availability and accessibility of health care resources, different lifestyle and poor network connectivity, an assumption for low risk for DM and DR was made in the current study. It was observed that the prevalence of DM was statistically high among low landers (12.3%) when compared to high landers (7.2%) (p < 0.001) with the high mean level of FBG among low landers (136.6 mg/dl) than high landers (101.1 mg/dl) areas. In the present study, about 60.0% among high landers and 40.0% among low landers were observed to be below 50 years of age, reflecting more of population with young age in high-altitude area when compared to low-altitude area. Among diabetics, about half of patients among high landers and about a quarter among low landers were below 50 years of age. Such type of supportive evidence was observed where about more than half of DM cases were

less than 50 years of age.[18] The high-altitude area (tribal area) in the current study was observed to have less prevalence for DM, which is in the observed range of evidence across the country. It may not be actually less but could be a marker for early appearance of chronic diseases in the tribal area.

Smoking increases the risk for DM and associated macro- and micro-vascular complications.[19,20] Smoking was found to cause substantial changes in insulin sensitivity among patients with non-insulin DM. A meta-analysis showed the prevalence of smoking was high among diabetic patients when compared to normal subjects.[21] Local evidence from a study conducted in the same state but in a different study area, observed that the prevalence of smoking among diabetics was about 10.0% in the urban and 4.0% in the tribal population.[22] The current study observed that among screened individuals for DM, there was low prevalence of smoking (8.5%) among high landers when compared to low landers (11.8%) (p < 0.001), but it was observed almost similar (about 10.0%-12.0%) among diabetics in both areas. However, in the low-altitude areas, significantly more screened individuals and diabetics were observed with smoking duration of more than 10 years and consumption of more than 10 cigarettes per day.

Hypertension is a common chronic morbidity associated with DM.[23] In India, the overall prevalence of hypertension is about 40.0%, more in urban (63.2%) than in rural (36.8%) areas and reportedly varies from 20.0% to 40.0% in urban and from 12.0% to 17.0% in rural India.[23] Hypertension and DM were observed as co-morbid conditions in a hospital-based study, as in diabetics hypertension prevalence was 60.2%, 76.5%, and 85.8% at blood pressure thresholds of 140/90, 130/85, and 130/80 mmHg, respectively.[24] Descriptive evidence from 10 states in India observed co-existence of DM and hypertension in 20.6% patients.[25] Another study from the same study area observed the prevalence of DM as 10.4% in stage-1 and 16.9% in stage-2 hypertension.[22] The current study observed that among all screened, hypertension was more prevalent among low landers: high prevalence of stage-1 hypertension among high landers and stage-2 hypertension among low landers. Among diabetics, the prevalence of stage-1 hypertension was found to be high in both areas, but stage-2 hypertension was significantly high in the high-altitude area. Overall, about 20.0% of the screened individuals were hypertensive, which is quite similar to study from central India that found hypertension in 19.4% of the population, but high when compared to 14.5% in the rural area of South India.

Surveys in developing countries suggest an early increase in the risks for chronic diseases like DM and hypertension.[26] The current study observed that there was high prevalence of hypertension, DM and DR among low landers in comparison to high landers, and being in the low-altitude area the OR for DM, hypertension and DR was twice as high than that of the high-altitude area. Evidence from Africa, China and the Pacific islands also documents that the risk-factor level increases when

people migrate to more urbanized settings.[21-25] In the present study, the degree of urbanization was not studied, but subjective, not objective, assessment of both the areas showed less urbanization in the high-altitude area when compared to the low-altitude area, which could be the reason for the observed differentials. The high-altitude area remains disconnected from the rest of the state in absence of rail, road and air transport, so, in itself it can be seen as a justification for the complete absence of urbanization. For the high-altitude area, though there was low prevalence of DR and relatively less prevalence for DM and HTN, the effect of urbanization in the coming times cannot be underestimated. So, it becomes important to establish an effective surveillance system to track the lifestyle changes within the community and measures to reduce the impact of urbanization.

There are limitations to the study, as the extent of urbanization was not studied objectively, and inferences drawn in the present evidence are based on the cross-sectional study. However, an effort was made to draw sufficient sample size in both areas to meet statistical assumption, although logistic regression was used as a multivariate statistical test which is robust to violation of assumptions. A far lower number of DR cases limits the statistical analysis, but there is sufficient evidence in favour of early onset of DM among high landers for regular screening and lifestyle interventions.

Acknowledgement

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