Diabetes in India—Existing trends, risk factors and emerging concerns

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1. Trends in prevalence of diabetes and its complications

1.1. Diabetes prevalence

The twin epidemic of type 2 diabetes and obesity is rising at alarming rates in India, and their additive effect on mortality and morbidity could be highly deleterious. As there is a close association between the pathogenesis of obesity and diabetes, the number of people with diabetes in India also started to rise gradually during 1980s and 1990s. Indeed, from the year 2000 onwards, there has been an explosion of the number of people with diabetes in India. Various state-specific surveys done in the past decade has shown a highly variable prevalence, but a definite increasing trend with figures from 5.0% to 20% [1-3].

There is an urban-rural divide in the prevalence of diabetes with the urban areas having highest prevalence, but the rural areas are fast catching up with the urban areas in terms of diabetes prevalence. Table 1 presents the multicentre studies on diabetes prevalence in India [3-8]. An ICMR-multicentre study based on questionnaire and self reported diabetes showed a rural prevalence of 3.1% [7] whereas Chow et al. reported a 13.2% rural prevalence [8]. Though these differences could be attributed to regional differences within India, it also clearly demonstrates that the urban-rural difference in prevalence of diabetes is fast disappearing at least in some parts of the nation like Kerala.

In recent years, there has been a sharp increase in the number of individuals with diabetes in the age group of 18-34 years. The NUDS [3] and CURES [10] studies showed that there has been a shift to the left in the age at diagnosis of type 2 diabetes, even within the 4-yr time period of these studies. Most of the currently available estimates of diabetes prevalence in India are regional and limited by small sample sizes. No study on diabetes has systematically sampled all the states in the country or even a single state completely. Thus, the Indian Council of Medical Research-India Diabetes (ICMR-INDIAB) study, which is a representative national survey, was conceived with the aim of obtaining the prevalence of diabetes and prediabetes in India as a whole, covering all the 28 states (now 29 States after the State of Andhra Pradesh was divided into Telangana and Andhra Pradesh), the National Capital Territory (NCT) of Delhi and two of the union territories (UTs) in India with a total sample size of 1,24,000
<table>
<thead>
<tr>
<th>Author/year</th>
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<td>Ahuja, 1991 [5]</td>
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<tr>
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<td>19754 1.9%</td>
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<td>Mohan et al., 2008 [7] (Only self reported diabetes)</td>
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<td>15239 11.2%</td>
<td>13524 9.6%</td>
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<tr>
<td></td>
<td>Dibrugarh</td>
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<td>5.5</td>
<td>0.6</td>
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<td></td>
<td>3.2</td>
<td>0.6</td>
</tr>
<tr>
<td>Anjana, R.M. et al., 2011 [8]</td>
<td>Tamilnadu</td>
<td>20+</td>
<td>1029 13.7%</td>
<td>2480 7.8%</td>
</tr>
<tr>
<td></td>
<td>Maharashtra</td>
<td></td>
<td>1093 10.9%</td>
<td>2476 6.5%</td>
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<td></td>
<td>Jharkhand</td>
<td></td>
<td>840 13.5%</td>
<td>2051 3.0%</td>
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<td></td>
<td>Chandigarh</td>
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<td>839 14.2%</td>
<td>2247 8.3%</td>
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</table>

individuals in a phased manner [8]. In addition, the study will provide a reliable nationwide data of related non communicable disease like obesity, hypertension, dyslipidemia, and coronary artery disease. Phase I of ICMR-INDIAB study included three states namely Tamil Nadu, Maharashtra, Jharkhand and one Union Territory namely Chandigarh located in the south, west, east and north of the country,
respectively. Phase II comprises the eight North-Eastern states namely Assam, Arunachal Pradesh, Manipur, Meghalaya, Tripura, Sikkim, Mizoram and Nagaland and Phase III involves the rest of the country. A stratified multi-stage sampling design has been adopted and 4000 individuals aged ≥20 years will be recruited from each state. Currently, Phase I of the study has been completed and Phase II and north east component is under progress. The ICMR-INDIAB study-Phase I, reported that the prevalence of diabetes (both known and newly diagnosed) to be 10.4% in Tamil Nadu (Urban – 13.7; Rural – 7.8%), 8.4% in Maharashtra (Urban – 10.9%; Rural – 6.5%), 5.3% in Jharkhand (Urban – 13.5%; Rural – 3.0%), and 13.6% in Chandigarh (Urban – 14.2%; Rural – 8.3%). The overall number of people with diabetes in India in 2011 was estimated to be 62.4 million [8] and this was similar to the IDF projection for India, which gave a figure of 61.3 million people with diabetes in India in the age group of 20-79 years [11].

Thus, the various epidemiological studies conducted in India, shows that the prevalence is higher in urban India and also increasing faster as compared to rural population. These studies show that there is a 10-fold increase in the prevalence of diabetes in India in both urban and rural areas over a 10-year period. The number of diabetic people in India has increased from 19 million in 1995 [12] to 32 million in 2000 [13] to 62.4 million in 2011 [8] and 66.8 million in 2014 [14]. These figures predict possible increase to 109 million by 2035 and even these are probably an underestimation [15].

In addition to this, India has a large pool of prediabetic subjects who have a high potential to develop type 2 diabetes. In the ICMR-INDIAB study, the weighted prevalence of prediabetes among urban residents of Tamil Nadu, Maharashtra, Jharkhand and Chandigarh was reported to be 9.8%, 15.2%, 10.7% and 14.5% and that among rural residents 7.1%, 11.1%, 7.4% and 14.7% respectively. Extrapolated to the whole country, these estimates translated 77.2 million with prediabetes in India in 2011 [8].

An increasing prevalence of diabetes in the youth is also observed. This early onset of type 2 diabetes is another worrisome aspect that calls for greater attention from the health care professionals as this means that by middle age, the burden of diabetic complications could be huge.

1.2. Burden of diabetes-related complications

Long-term complications of diabetes affect almost every system in the body, particularly the eyes, kidneys, heart, feet and nerves. Diabetes-related vascular complications can be broadly classified as: (a) Microvascular complications affecting the retina (diabetic retinopathy), kidney (diabetic nephropathy) and the peripheral nerves (diabetic neuropathy); and (b) Macrovascular complications which affect the heart (cardiovascular disease), brain (cerebrovascular disease) and the peripheral arteries (peripheral vascular disease).

1.2.1. Diabetic retinopathy

Diabetic retinopathy (DR) is considered as the most specific complication of diabetes and indeed one of the hallmarks of the disorder. DR is the leading cause of new onset blindness, among adults in developed countries and is rapidly becoming so in developing countries also. DR affects the microvasculature in the retina, or the back portion of the eye. The classification of DR has evolved as the understanding of the disease has improved. DR is classified into two major types or stages: Non-proliferative DR (NPDR) and Proliferative DR (PDR). The sight-threatening forms are PDR and Diabetic Macular Edema (DME) – retinal thickening and/or exudates within 500m of the retina (macular). The CURES Eye study used four-field stereo retinal photographs and ETDRS grading to document DR in the Indian population. The
overall prevalence of DR in urban population in this study was 17.6% [16]. The Sankara Nethralaya Diabetic Retinopathy Epidemiology and Molecular Genetic Study (SN-DREAMS) conducted in Chennai reported a DR prevalence of 18% [17].

1.2.2. Diabetic nephropathy

Diabetic nephropathy is the leading cause of end-stage renal disease (ESRD) worldwide [18]. Kidney disease in diabetic patients is clinically characterized by increasing rates of urinary albumin excretion, starting from normoalbuminuria which progresses to microalbuminuria, macroalbuminuria and eventually to end stage renal disease. Microalbuminuria is the earliest clinically detectable stage of diabetic kidney disease at which appropriate interventions can retard, or reverse, the progress of the disease [19]. CURES is the first population based study from India to report on prevalence of diabetic nephropathy. This study showed that the overall prevalence of overt nephropathy was 2.2% while that of microalbuminuria was 26.9% [20]. The CRDPP (Chunampet Rural Diabetes Prevention Project) study documented a prevalence of microalbuminuria among rural population in Tamil Nadu to be 24.3%, which is similar to that found among the urban population in CURES [21].

1.2.3. Diabetic neuropathy

Diabetic neuropathy affects nearly 50% of all diabetic subjects and is considered to be the main cause for morbidity. The intensity and extent of the functional and anatomical abnormalities of diabetic neuropathy parallel the severity and duration of hyperglycemia [22]. Among individuals with diabetes, neuropathy is a common cause of morbidity (painful polyneuropathy, neuropathic ulceration) and mortality (due to autonomic neuropathy) presenting a huge economic burden to society [23]. A surprisingly high prevalence of 64.1% was reported in a diabetic outpatient clinic at Bangalore in the year 2006 [24]. In a multicentric study from Chennai, Madurai, Vellore and Delhi, conducted in a total of 1319 type 2 diabetic patients, the prevalence of neuropathy was reported to be 15%. There are very few population based studies on diabetic neuropathy in India. A prevalence of 30.9% was reported in the CRDPP study in rural Tamil Nadu [21].

1.2.4. Coronary artery disease

Diabetes mellitus is an independent risk factor for cardiovascular disease. Prevalence of coronary artery disease (CAD) is also increasing at an alarming proportion in India. The present prevalence of this disease among Indians ranges from 9% to 14% [25]. The various risk factors identified for cardiovascular disease include aging, smoking, strong family history of CAD and diabetes and life style related factors like physical inactivity and stress. The Interheart study conducted in 52 countries demonstrated that over 90% of the population attributable risk of acute myocardial infarction (AMI) were accounted for by nine modifiable risk factors, which included smoking, diabetes, hypertension, abdominal obesity, the ApoB/ApoA1 ratio, psychosocial stress, decreased fruit and vegetable intake, physical inactivity, and regular alcohol consumption [26, 27].

1.2.5. Peripheral vascular disease

Peripheral vascular disease (PVD) in diabetic patients differs from that seen in non-diabetic individuals. In non-diabetic individuals the sites of occlusion are more proximal usually the infra-renal aorta, iliac and superficial femoral arteries, with sparing of distal vessels whereas in diabetic patients, occlusive lesions occur in more distal vessels such as the tibials and peroneals. The Chennai Urban Population
Study (CUPS) was the first population-based study to report on prevalence of PVD in India. It reported that the prevalence of PVD was 6.3% among diabetic subjects as compared to 2.7% among non-diabetic subjects [28] confirming that the prevalence of PVD is low in Indian population. It may also be due to the younger age of onset of type 2 diabetes in India.

1.2.6. Cerebro vascular disease

Strokes are the third commonest cause of mortality in diabetic patients after heart disease and cancer and represent a major health burden in India [29]. In a study conducted in Asian Indians living in the United States, prevalence of stroke was significantly associated with systemic hypertension, diabetes CAD, end-stage renal disease, and family history of stroke and myocardial infarction [30]. To curb the rising trend of stroke in India, the two principal risk factors i.e. hypertension and diabetes mellitus need to be tightly controlled. Change in dietary habits to reduce intake of fat and salt and a complete cessation of smoking and chewing tobacco also need to be encouraged.

2. Risk factors

2.1. Nutritional and lifestyle changes

2.1.1. Urbanization and sedentariness

Nations adopting a westernized life style have caught up fast with the alarming trend of diabetes explosion and the effect of environmental influences such as diet and physical activity leading to obesity has a crucial role in the pathogenesis of insulin resistance and diabetes. People living in the urban areas have higher abdominal obesity and sedentary behaviour showed 11.3% of self reported diabetes, whereas residents in the rural areas performing vigorous activity without abdominal obesity showed 0.7% of self reported diabetes as shown by a nationwide NCD risk factor surveillance study involving a total of 44,523 subjects [7]. Factors like marital status, housing, smoking, exercise, diet, drinking and occupation all together accounted for over 75% risk of the overall variation in the waist-hip ratio in Asian Indians and this point towards the implicit role of urbanization and westernization in obesity [31].

The results of phase-1 of the ICMR-INDIAB study showed that out of 14,227 individuals studied, 54.4% were inactive, 31.9% were active and 13.7% were highly active. 65% subjects were more inactive in urban as compared to 50% in the rural areas [32]. Since physical inactivity is a modifiable risk factor for diabetes, it is considered as the cornerstone of diabetes management. Various reports have shown an improvement in diabetes status after intervention with physical activity. The Chennai Urban Population Study (CUPS) was an epidemiological study which showed a significantly higher prevalence of diabetes in middle income colony (12.4%) as compared to lower income group (6.5%). An intervention programme in the middle-income colony significantly improved knowledge and physical activity levels and this was evident in the increased percentage of residents who exercised from 14.2% to 58.7%, representing a 300% increase in physical activity. A follow-up study was conducted 10 years after the diabetes education programme to assess the new diabetes prevalence rates in the same two colonics. During this period, in the lower income group, the prevalence of diabetes increased from 6.5% to 15.4% (a 135% increase) whereas in the middle-income group, the prevalence increased from 12.4% to 15.4% (24% increase) [33]. This project indicates that a moderate investment of time and effort might arrest the rapid rise in the prevalence of diabetes.
2.1.2. Dietary changes

India occupies a primary position in the list of nations experiencing the nutritional transition and this has resulted in the consumption of excess calories, simple sugars, saturated and trans fatty acids and lower consumption of fibre. These dietary changes along with physical inactivity have resulted in the escalation of obesity rates [34]. When Indian and the American adolescents were compared with respect to the intake pattern of food, lipid profile, micro and macro nutrients, the Asian Indians exhibited a higher level of total fat, lower omega-3 PUFAs, MUFA and higher SFAs as compared to their American counterparts. This pattern might explain the increased prevalence of obesity and insulin resistance in the Asian Indian adolescents living in the urban areas [35]. Mohan et al. (2014) have shown that improving the quality of carbohydrate by replacing the staple white rice with brown rice has beneficial effects on reducing the risk for diabetes and related complications [36]. Deficiency of vitamin D and vitamin B12 have been shown to be closely associated with diabetes. In a comparative study involving Europeans and Indians, the prevalence of vitamin B12 deficiency was 27% and 12% respectively [37].

2.1.3. Obesity

The prevalence of type 2 diabetes increases with age and increasing visceral or abdominal obesity. It is well known that type 2 diabetic subjects are often obese and alternatively, obese subjects are likely to have insulin resistance. The link between obesity and diabetes may be accelerated due to the transition from an active rural to sedentary urban socioeconomic milieu. Though studies have shown both total fat and visceral fat to be associated with diabetes, visceral fat is considered to be more important as it has been shown to have a strong correlation with glucose intolerance and insulin resistance. The visceral fat stored beneath the muscles and wrapped around the internal organs is considered to be the most ‘atherogenic’, ‘diabetogenic’ and ‘hypertensiogenic’ fat depot of the human body [38]. However, high prevalence of excess body fat, adverse body fat patterning, hypertriglyceridemia, and insulin resistance beginning at a young age have been consistently recorded in Asian Indians irrespective of their geographic location [39]. Indians also have peculiar characteristics known as the ‘Asian Indian phenotype’, which increase their susceptibility for diabetes. Despite having lower prevalence of obesity as defined by body mass index (BMI), Asian Indians tend to have greater waist circumference and waist to hip ratio thus having a greater degree of central obesity [40]. Again, Asian Indians have more total abdominal and visceral fat for any given BMI and for any given body fat they have increased insulin resistance.

Abdominal obesity is found to be highly prevalent in Asians at younger age and a lower BMI (below 25 kg/m²). When parameters like distribution of fat, body size and body fat were compared in young men of New Zealand European, Pacific Island, and Asian Indian populations, it was found that in Asian Indians, the association between body fat percentage and BMI was different from that of the other ethnic group. This could be partially because of the differences in musculature as abdominal fat deposition is found to be higher in Asian Indian than the other ethnic groups [41]. Figure 1 shows the relation between the occurrence of obesity and type 2 diabetes.

2.2. Genetic susceptibility

There are some ethnic groups who have a specific predisposition on the basis of their genetic make up to develop diabetes depending on their exposure to adverse conditions and topping the list are the Hispanics and the Asian Indians. The thrifty gene hypothesis argues that a culmination of polymorphisms or genetic defects led to a genetic advantage in certain populations which makes them susceptible to
insulin resistance and diabetes when there is plenty of food supply. Mutations at multiple sites that are correlated with minute changes in insulin sensitivity together could lead to a decrease in insulin sensitivity [42]. A parental history of type 2 diabetes has been shown to increase the risk of overweight, higher LDL cholesterol, glucose intolerance and high blood pressure in the offspring [43]. Table 2 summarizes the genetic polymorphism studies done on Asian Indians in relation to obesity and type 2 diabetes [44-54]. Genome wide association studies of type 2 diabetes showed that in individuals of South Asian ancestry, 20 independent SNPs associated with T2D were identified [55]. Recently, another replication and meta-analysis study involving multiple ancestry groups like European, East Asian, South Asian, Mexican and Mexican American ancestry identified seven novel loci for T2D susceptibility [56].

2.3. Intra-uterine environment, maternal nutrition and the thin-fat Indian baby

In Asian Indians, the first study on the fetal origins was conducted in Pune, which investigated the low birth weight as an independent predictor of insulin resistance [57]. On measuring parameters associated with glucose tolerance and insulin resistance in 4-8 year old children, it was found that circulating concentrations of glucose and insulin are associated strongly to the child’s present size. On follow up, when the confounding effect of the child’s current size was removed, an inverse association between the birth weight and the circulating insulin and glucose levels was evident.

Overnutrition in the intra-uterine environment has also been shown to predict the development of diabetes in Asian Indians. It has been shown by Fall et al. [58] that birth weight dictates higher waist, BMI and skin fold thickness during middle age. Also a higher ponderal index or shorter length has been shown to predict the development of diabetes, though this relationship has not been reported in case of
Europeans. Hence the birth size and the skin fold thickness of the Indian baby is predicted by means of the size of the mother. Mothers who are short and fat and who gained weight in pregnancy gave birth to the fattest babies. Physical activity of the mother and the systemic levels of folate and ferritin were also found to have an inverse association with the skin fold thickness of the baby [59].

Table 2. Genetic polymorphisms associated with type 2 diabetes and obesity

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<td>Ramya, K. [44]</td>
<td>1,852</td>
<td>FTO</td>
<td>The rs9940128 A/G, rs11076023 A/T, and rs1588413 C/T associated with T2DM, rs8050136 C/A variant was associated with obesity.</td>
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<tr>
<td>Vimaleswaran, K.S. [45]</td>
<td>4000</td>
<td>Adiponectin gene</td>
<td>There is an association of +1021 T-&gt;G polymorphism in the first intron of the adiponectin gene with type 2 diabetes, obesity and hyperadiponectinemia.</td>
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<td>Vimaleswaran, K.S. [46]</td>
<td>1500</td>
<td>(PPARGC1A), (PPARG), (UCP1) gene</td>
<td>Thr394Thr variant of the PPARGC1A gene was significantly associated with diabetes and obesity. Polymorphisms in the PPARGC1A, PPARG and C1P genes are not associated with MS in Asian Indians.</td>
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<tr>
<td>Radha, V. [47]</td>
<td>1350</td>
<td>LPL gene</td>
<td>The -T93G SNP of the LPL gene is associated with obesity whereas the -G53C SNP appears to be protective against both obesity and type 2 diabetes.</td>
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<td>Bodhini, D. [48]</td>
<td>2211</td>
<td>IRS-2</td>
<td>DD genotype increases susceptibility to type 2 diabetes by interacting with obesity.</td>
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<td>Been, L.F. [49]</td>
<td>3,310</td>
<td>KCNQ1 gene</td>
<td>Variation within the KCNQ1 locus confers a significant risk to T2D among Asian Indians.</td>
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<td>Yajnik, C.S. [50]</td>
<td>3775</td>
<td>FTO</td>
<td>A strong association of the minor allele A at rs9939609 with type 2 diabetes.</td>
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<td>Been, L.F. [51]</td>
<td>1528</td>
<td>MC4R and MLX interacting protein-like (MLXIPL) perilipin (PLIN) locus</td>
<td>Genetic variation in MC4R locus can have a moderate contribution in the regional fat deposition and development of central obesity in Asian Indians. PLIN 14995A&gt;T SNP is the most informative single genetic marker for the observed haplotype association, being significantly associated with increased obesity risk in both Malays OR 2.28 (95% CI 1.45-3.57) and Indians.</td>
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<tr>
<td>Qi, L. [52]</td>
<td></td>
<td>LPL</td>
<td>The association between the X447 allele and serum HDL-C concentration was modulated by APOE genotype in males. The effect of the X447 allele was greatest in men who carried the E4 allele and women who smoked or consumed alcohol. The epsilon 2 allele was the least common in Asian Indians. Asian Indians had the lowest HDL-C for each APOE genotype except in Asian Indian males with epsilon 2, where HDL-C concentrations were intermediate between Chinese and Malays.</td>
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<td>Lee, J. [53]</td>
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<td>Tan, C.E. [54]</td>
<td>2475 chines 687 malays 528 AIs</td>
<td>APOE</td>
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3. Emerging concerns and newer etiological factors

3.1. Organic pollutants and diabetes

Recent research has indicated a role of persistent organic pollutants (POPs) in diabetogenesis by acting as endocrine disrupting chemicals. Chronic accumulation of these environmental pollutants in small concentrations in the body has been shown to be associated with type 2 diabetes, obesity and metabolic syndrome. The obesogenic and diabetogenic effect of POPs has been elegantly demonstrated in a report by Dirinck et al. (2014) which showed that the accumulation of several pollutants in the adipose tissue of obese and diabetic individuals were higher than their normal counterparts and the serum levels of polychlorinated biphenyls were significant predictors of abnormal glucose tolerance [60]. A 25-year follow up study done on subjects exposed to dioxin, due to an industrial accident in Italy, has shown significant higher rates of mortality from diabetes mellitus [61]. Further, these pollutants have been proposed to modulate insensitivity and beta cell function by inducing chronic low grade inflammation, depletion of anti-oxidants and by affecting the function of mitochondria. Large prospective studies that screen the vast array of POPs are clearly required to arrive at the environmental pollutants that are most relevant to diabetes occurrence [62]. Also, lifestyle changes involving healthy and nutritious food rich in antioxidants and bio-active nutrients might help in reducing the vulnerability of the body to such environmental stressors.

3.2. Overlap between communicable diseases and diabetes

A higher prevalence of diabetes has been observed in middle and low income nations where TB is endemic. Hence there is a lot of research focus on elucidating the potential mechanical links connecting TB and diabetes. There are studies showing higher risk of TB in patients with diabetes and vice versa. Several studies from Asia have shown that type 2 diabetes patients are associated with a higher risk of tuberculosis after adjusting for confounders and therefore the diabetes epidemic might fuel TB resurgence in endemic regions [63, 64]. In a study carried out in Chennai, DM prevalence was 25.3% in TB patients and risk for diabetes mellitus was higher among sputum positive pulmonary TB patients [65].

4. Conclusions

India ranks second in the global diabetes epidemic and is experiencing a shift in the diabetes epidemic from urban to rural areas, the affluent to the less privileged and from older to younger people and even children. It is worrisome that there are high prevalence rates of diabetes not only in urban areas but also in rural areas in India. This is due to rapid epidemiological transition involving globalization, changes in dietary habits and decreased physical activity (Fig. 2). This transition from traditional to modern life has several health hazards including the development of non-communicable diseases like diabetes. Nearly 70% of the Indian population lives in villages whereas 80% of specialist doctors practice in urban areas. This serious mis-match means that specialized health services are not available to the rural poor and when available, are not affordable. This leads to significant morbidity and mortality associated with micro and macro vascular complications. Unless urgent preventive strategies are introduced, the diabetes epidemic could overwhelm the economy of the country. A particularly disturbing trend currently observed in India is the shift in onset of diabetes to younger ages. In India, earlier studies have shown
that people belonging to the high and middle income group are shown to have higher prevalence rates of diabetes as compared to the lower income group. Unfortunately, the disease has now started affecting the lower strata of the society. This means that while the rich could have better access to diabetes care, the poor would be unable to afford treatment and therefore likely to suffer from more complications. This calls for urgent steps to prevent diabetes using a multisectoral approach. The time to act is NOW!

Acknowledgements

We thank the epidemiology team of Madras Diabetes Research Foundation for the fieldwork and most importantly the subjects who participated in all our studies.

REFERENCES


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