Type 2 Diabetes Express Highway, Where is the ‘U’ Turn?

SR Iyer

Abstract
The ‘U’ turn in Type 2 Diabetes Express Highway probably lies in lifestyle modifications - going back to traditional lifestyle with use of modern technology to achieve happiness. There is a difference between technology for comfort and technology for happiness.

INTRODUCTION
The accounts of polyuria can be traced back to Egyptian Papyrus (1500 BC). The lane of diabetes mellitus was discovered in tropical India around 600 BC, just prior to the Buddhist era. This lane was narrow one. Both Charak and Susrutha described the sweetness of urine (madhumeha, honey urine) in some patients with polyuria. Hastimeha is also described in Ayurvedic literature where a patient passes excessive urine like an excited elephant. This has relation to diabetes insipidus.

The prevalence of diabetes is increasing globally. This is probably a price we are paying for the progress, urbanization and fast paced life. The World Health Organization estimated that there were 135 million diabetic individuals in the year 1995 and it has projected that this number will increase to 300 million in 2025. Major contribution will be from developing countries particularly India. Revised diagnostic criteria have clearly defined impaired glucose tolerance. Recognition of these subjects is important since they are very likely to develop diabetes. Moreover lifestyle modifications and pharmacological interventions have major role to play in preventing diabetes.

Insulin resistance and hyperinsulinemia occupy a central stage of diabetes which leads to abnormalities of glucose metabolism and is present much before the metabolic abnormalities are manifested. Studies have shown that Asian Indian patients with non-insulin dependent diabetes (type 2 DM) are more insulin resistant than their European counterparts.

Today India has the largest number of diabetic individuals. It is estimated that there are approximately 19.4 million diabetic individuals in our country (quoted in 1995) and this is expected to touch 57.2 million in the year 2025. However today there may be approximately 25 million diabetic individuals. It will not be a wonder if the coming generations lose sight of typical Indian village and its lifestyle. Today urban areas, urbanizing areas and rural areas can be mapped out in our country. This has a bearing in the development of lifestyle diseases. Diabetes is one of them. Diabetes (type 2 diabetes) has been labelled as lifestyle disease, metabolic disease, vascular disease or simply cardiovascular disease.

RISING PREVALENCE OF DIABETES
Several prevalence studies indicate that the diabetic lane has gradually transformed into an ‘Express Highway’. Till 1970 the prevalence of diabetes was considered to be low. In 1959 Patel et al reported an incidence of 0.8% from Bombay, while Berry et al, Srivastava et al, Gupta et al, Ahuja, reported 2.91%, 2.84 and 2.1% from Chandigarh, Jabalpur, Ahmedabad and New Delhi respectively. In a study conducted at Bardoli in 1979, we reported a prevalence of 4.4%. Bardoli is a taluka place (urban town) in Surat district where farming is the main occupation. Diamond cutting is the other industry in this area. Most of the villages around Bardoli are partly urbanized. The economic status of persons in this is area is good due to good income from sugarcane farming and business abroad (many motels in USA and Canada are owned by the residents around Bardoli). Sugarcane farming is comparatively easier and more economically viable. The high prevalence of diabetes is due to good economic status, sedentary lifestyle (even visit to the farms is usually on motor bikes) and consumption of oil-rich food. Groundnut eating is a common practice. It is known that those individuals who enjoy sedentary life suffer from hypokinetic stress. Even diamond cutters are sedentary workers. They sit for long hours around a circular table. Hypokinetic stress is an instinctual stress (Instinctual stress is caused by deprivation of instincts. The different
instincts are survival, hunger, thirst, sleep, sex, movement, parenteral care, herd and habitat. The stress which is caused by confinement to place with denial of movement is called hypokinetic stress. Although the villages are partly urbanized, the stress of travel is not much experienced since the place of work is near to the place of stay and the distance is usually covered on automobile.

Table 1 shows the prevalence of diabetes in India from 1959 as reported by various authors. It is clear the prevalence is on the rise all over the country.

<table>
<thead>
<tr>
<th>Year</th>
<th>Author</th>
<th>Place</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1959</td>
<td>Patel et al.</td>
<td>Bombay</td>
<td>0.8</td>
</tr>
<tr>
<td>1966</td>
<td>Berry et al.</td>
<td>Chandigarh</td>
<td>2.91</td>
</tr>
<tr>
<td>1966</td>
<td>Srivastava et al.</td>
<td>Jabalpur</td>
<td>1.70</td>
</tr>
<tr>
<td>1970</td>
<td>Gupta et al.</td>
<td>Ahmedabad</td>
<td>2.84</td>
</tr>
<tr>
<td>1972</td>
<td>Ahuja</td>
<td>New Delhi</td>
<td>0.9</td>
</tr>
<tr>
<td>1979</td>
<td>SR Iyer et al.</td>
<td>Bardoli</td>
<td>4.4</td>
</tr>
<tr>
<td>1988</td>
<td>Ramchandran et al.</td>
<td>Kudremukh</td>
<td>5.0</td>
</tr>
<tr>
<td>1992</td>
<td>Ramchandran et al.</td>
<td>Chennai</td>
<td>8.2</td>
</tr>
<tr>
<td>1997</td>
<td>Ramchandran et al.</td>
<td>Chennai</td>
<td>11.6</td>
</tr>
<tr>
<td>2000</td>
<td>Mohan et al.</td>
<td>Chennai</td>
<td>12.0</td>
</tr>
<tr>
<td>2000</td>
<td>Kuttty et al.</td>
<td>Thiruvanthapuram</td>
<td>12.4</td>
</tr>
<tr>
<td>2001</td>
<td>Misra et al.</td>
<td>New Delhi</td>
<td>10.3</td>
</tr>
<tr>
<td>2001</td>
<td>Ramchandran et al.</td>
<td>Six urban citis</td>
<td>12.1</td>
</tr>
<tr>
<td>2001</td>
<td>SR Iyer et al.</td>
<td>Dombivli</td>
<td>7.5</td>
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<td></td>
<td>(Dist. Thane)</td>
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</table>

What is the cause of the rising prevalence? Should we be satisfied with risk factors mentioned in western literature and whether controlling them will suffice? The recognized risk factors for type 2 diabetes described in western literature are family history of diabetes, obesity, age ≥ 45 years, race/ethnicity, previously identified impaired fasting glucose or impaired glucose tolerance, history of gestational diabetes, history of delivery of large babies, hypertension (BP ≥ 140/90 mm Hg), low levels of HDLc (≤ 35 mg/dl) and or increased triglyceride levels (≥ 250 mg/dl) and polycystic ovary syndrome. Asian Indians have strong familial aggregation of diabetes with high prevalence of diabetes among the first degree relatives and vertical transmission through two or more generations. Are there any unrecognized factors in India and whether they have a bearing in the development of type 2 diabetes?

**STRESS**

Stress has a major role to play in the causation and progress of diabetes, particularly in developing countries like India. Stress is defined as a state of threatened homeostasis. Stress itself is not bad and to an extent is necessary for maintaining life. Not all stressors have identical response. It depends upon genetic, environmental and lifestyle factors. It is important to differentiate between stress hyperglycemia and stress-induced diabetes. Stress hyperglycemia is catecholamine-mediated response to circulatory failure.

There are several observations to show that stress is directly linked to development of obesity and diabetes. Psychological stress has a bearing on the development of diabetes or worsening of glycemic status. Chronic environmental stressors are basically a result of fight for survival and progress. This is aggravated when too much is desired in too little time. In any society, adversity, social instability and conflicts accelerates pathophysiological processes resulting in increased morbidity and mortality. Animal experiments have demonstrated that long term stress accelerates a number of biological markers of ageing.

Certain stressors affecting a large section of Indians residing in India are unique and it is worth mentioning a few. (i) Water scarcity: This demands great time management from all members in the family particularly from women. (ii) Fear of losing employment in the face of economic recession. (iii) Overtime working and late hours in office. (iv) Travelling on Sunday’s and holidays is significant stress not only for the workers but also in family members. (v) Lack of uninterrupted power supply in several parts of country. (vi) Lack of uninterrupted power supply in several parts of country. (x) The replacement of joint families by nuclear families is reflected in poor care of elderly homes in the country. (xi) Overtime working and late hours in office. (xii) Fear of losing employment in the face of economic recession. (xiii) Overtime working and late hours in office. (xiv) Lack of uninterrupted power supply in several parts of country. (xv) Lack of uninterrupted power supply in several parts of country. (xvi) Burden of education in students of both schools and colleges. There is a constant fear of not able to secure admissions in desired colleges, colleges and universities. In education, if there is no provision or inadequate provision of physical activity, locomotion and psychomotor activity then it may have variable influence on the student leading to hypokinetic stress. (xvii) The replacement of joint families by nuclear families is reflected in poor care of elderly resulting in stress in the family. The mushrooming of several elderly homes in the country is a reflection of this problem.

**HOW STRESS CAUSES DIABETES?**

Allostasis or stability through change is an adaptation process in the face of potentially stressful challenge. Physiologic response of autonomic nervous system, hypothalomopituitary axis (HPA), cardiovascular, metabolic and immune system are involved in these phenomenon. Allostatic load is the wear and tear on the body and brain as a result of chronic overactivity or inactivity of physiological systems that are normally involved in the adaptation to environmental challenge. Allostatic load comes at a price when allostatic systems are either overworked or fail to shut off after the stressful event. The frequency and the intensity of stress determines the allostatic load. It should be appreciated that the concepts of stress are subjective and there are individual variations in coping the stress.
are several interacting adaptive systems of the body. If there is chronic activity or inactivity of the metabolic system (activating and maintaining energy reserves including energy supply to brain) it results in obesity, diabetes and atherosclerosis.

Stress results in increased production of cortisol. There is close association between cortisol and obesity. Cortisol directs storage fat to central adipose tissue depots, central obesity is an important feature of syndrome X. Central adiposity has also been called as the Cushing’s disease of the omentum. Constant exposure of glucocorticoids specifically to adipose tissue may be responsible for central adiposity. Cortisol apart from directing stored fat to face neck and trunk also favors neoglucogenesis, decreases protein synthesis, causes atrophy of lymphoid tissue, decreases eosinophils, decreases lymphocytes and macrophages, decreases interleukin-1 and interleukin-2 and stimulates suppressor cells. These effects increase the susceptibility to infections which themselves act as stressor (see later). Eosinopenia promotes parasite invasion.

Bjorn top’s hypothesis postulates that psychosocial stress triggers the onset of visceral obesity, insulin resistance and dyslipidemia. Stress not only results in increased production of cortisol but also its increased clearance. The HPA axis is more active in centrally obese men and centrally obese women but not postmenopausally. HPA activation may occur even in utero. Increased waist-hip ratio is a symptom of chronic hypothalamic arousal. The Hoorn study findings were partially consistent with Bjorn tops hypothesis; stressful life events were associated with undetected type 2 diabetes and visceral adiposity.

Misuse of corticosteroids is not uncommon in medical practice. Subjects exposed to steroid medication, indicated and unindicated for long periods run the risk of developing diabetes. Also experimental studies have demonstrated that prenatal exposure to glucocorticoids results in low birth weight babies permanent elevation of blood pressure and hyperinsulinism. In humans low birth weight is associated with elevated glucocorticoid levels in later life. Approximately 28% of children born in India are of low birth weight. Low birth weight with stunting and muscle wasting followed by over weight and obesity in later life form a major contributory factor for diabetes and insulin resistance syndrome.

Hypokinetic stress has its implications in predisposing a huge section of society viz. students, traders, clerks, cobbler and others to obesity and diabetes. Over the course of time the sedentary lifestyle is accepted as a routine. One may adopt modern lifestyle but may not adapt to it (Eating high caloric food should be coupled with good physical activity but often this is not practiced). Parenteral care is affected in working women and this generates stress in both in mother and the child. Also premature discontinuation of breast feeding may result in schizoid behaviour in the mother.

Psychiatric disorders like anxiety and depression may be associated with excessive food intake and resultant obesity. The overall lifetime prevalence of depressive disorder is 5-12% in men and 10-25% in women. Lifetime prevalence of panic disorder is 3.5%. There is reactive eating due to stress and anxiety. Binge eating is motivated by a desire to escape from self-awareness. Leptin is a fat hormone that regulates sex and metabolism. This metabolic modifier is closely linked to cortisol. Stress and high calorie diet are interlinked. Groundnuts are relatively inexpensive and are consumed excessively in tropics. It has high content of fats, carbohydrates, proteins and calories. 15 gram of groundnuts gives approximately 100 calories. Anxiety and depression may promote groundnut eating particularly in lower middle class. Potato chips & cashew nuts are common alternatives to groundnuts. It is also known that depressed individual have reduced physical activity.

Obsessive-compulsive disorder (OCD) is widely prevalent. The overall lifetime prevalence of OCD is 2-3%. Mean age of onset of OCD in India is in late 20’s and out of the total number approximately 25% may continue to suffer for many years. Considerable stress is experienced by subjects suffering from OCD.

Infections are abundant in our country. Chronic infections are source of internal stress. Entamoeba histolytica infestation is common in our country. The prevalence is 2-60% in different parts of the world. High prevalence has been observed in China, South East Asia, West Asia Latin America especially Mexico. Surprisingly the prevalence of DM is also high in these areas. In India the prevalence of amoebiasis is 15% (range 3.6-47.4%). Chronic inflammation is known to act as a trigger for chronic insulin insensitivity. I therefore propose that chronic infections are a source of chronic internal stress leading to development of obesity and diabetes. It will be interesting to explore the link between communicable and noncommunicable diseases.

Once diabetes sets in it serves as stress to the patient by way of diet control, mealt ime planning, medications and fear of complications.

**Nutrition**

Both undernutrition and overnutrition have been implicated in the causation of diabetes. Apart from quantity and quality of food, proper timings of food intake may not be maintained for various reasons. Fast paced modern life may deprive an individual of normal dietetic habits. For e.g. leaving to place of work very early in the morning may deprive the subject of breakfast. This may promote binge eating at office lunch hours (the lunch hour is usually of half an hour duration).

Traditional Indian food is served at ground level and the dinner seats in a specific posture which promotes digestion. Also the food consumption is monitored by the server. This prevents overeating and wastage of food. In contrast, buffet eating runs the risk of overeating, disturbed eating (eating disturbed by talking) and wastage of food at many occasions. Also talking while eating causes dyspepsia and indigestion. It is unfortunate that there is plenty of food in the country.
yet malnutrition-modulated diabetes mellitus (MMDM) is observed. Tripathy et al have reported that malnutrition plays a role in the development of MMDM. At the other end of the spectrum is overnutrition; consumption of high energy dense food and fat-rich fast food are risk factors for diabetes. The highest prevalence of diabetes is observed in populations that subsisted on low calorie restricted diet before being exposed to an abundance of food. The Pima Indians, North America and Australian aborigines when adopt western lifestyle develop high prevalence of diabetes. Epidemiological studies done in different parts of the world brought out an interesting finding that Indian migrants who were settled abroad have higher prevalence of diabetes. In a similar way in India, villagers when settle in cities also run the risk of developing obesity, diabetes and other lifestyle diseases.

Alcohol provides additional calories and it’s consumption has increased in the country. Alcohol forms an important ingredient of celebrations, parties, and business deals. Adoption of western line or modern lifestyle, brings in high caloric celebrations in pleasant moments. These pleasant moments may be created opportunities and frequent whereas in traditional Indian culture it was practically restricted to festivals.

**SMOKING**

Smoking is an independent risk factor for diabetes and smoking cessation is advisable. It must be noted that cessation of smoking often results in increase in body weight due to increased appetite.

**PHYSICAL ACTIVITY**

Physical activity of even moderate intensity and duration can reduce the risk of developing type 2 diabetes. Except those subjects who are morbidly obese, the way to achieve acceptable body mass index is by losing fat and not by losing weight. This should be achieved by increasing activity rather than by using weight reducing drugs. It is important of differentiate between exertion and exercise. Walking to railway station or to place of work in a stressed manner is not true exercise. Hypokinetic stress is experienced by subjects who have to travel standing or sitting daily for long hours to place of work and back home.

**SLEEP APNEA**

Sleep disorders are common in diabetic subjects. Polyuria, Nocturia, anxiety, depression due to the disease often disturb the sleep patterns. Recently sleep apnea has been linked to diabetes. Patients of obstructive sleep apnea (OSA) are prone to develop diabetes. Obesity is a risk factor for both diabetes and OSA. The fat around the neck squashes the upper airway. Lean subjects who have reduced posterior airway space because of retruded mandible or maxilla and an inferiorily positioned hyoid bone are also at risk of developing OSA. Therefore OSA is a risk factor for low body weight type 2 DM also. The prevalence rate of OSA is a approximately 2% in middle aged women and 4% in middle aged men. In India, Udwadia has reported the prevalence of OSA as 7.5% on the basis of apnoea hypopnoea index (AHI >5 per hour) and accompanying day time sleepiness while it is 20% on basis of AHI alone in middle aged Indian men between 35-65 years (personal communication). Snoring can be observed in sleeper coaches of trains and also in groups of people sleeping together in pilgrimage tours etc. Sleep study (polysomnography) though available in several major cities of India, is cost prohibitive. Even if OSA is diagnosed, the titration study and continuous positive airway pressure machine put an additional burden of Rs.60,000/-. The pathophysiological basis of association of OSA with diabetes rests on several hormonal changes which are triggered off with apnea. Repetitive apneas result in catecholamines release which remain elevated throughout the day. Catecholamines predispose toward hyperinsulinemia by stimulating gluconeogenesis and glucagons secretion, cortisol levels are also raised causing glucose intolerance insulin resistance and hyperinsulinemia. Excessive day time sleeping in patients of OSA promotes physical inactivity and thus increases body mass index. Patients of OSA have difficulty in maintaining optimal body weight. The role of circadian rhythm and catecholamines have their own role to play. OSA subjects also have a greater prevalence of calcified carotid artery atheromas. It must be emphasised that snoring is not a sign of sound sleep and central obesity is not a sign of prosperity. Hypoxemia of sleep apnea can be further deleterious in diabetics since there is reduced oxygen in uncontrolled diabetics. Exercise in diabetic subjects improves the glycemic status (reduction in HbA1c). This results in better oxygen delivery to tissues. It must be appreciated that the retina is the highest oxygen consuming part of the body. It needs to be explored whether hypoxemia due to any cause has an effect on retinal tissue and also a role in the development of diabetic retinopathy.

Heat shock proteins (HSP) are detected in all cells and are cytoprotective. Heat shock protein-72 decreases during sleep in patients with OSA and returns to normal with treatment on continuous positive airway pressure (CPAP). Such treatment also helps to attain optimal body weight. The impaired autonomic stress responses are also normalized by CPAP. The hypoxia in OSA have deleterious effects at the cellular level and it would be interesting to know its role in the development of vascular complications in diabetic subjects. There appears to be close association between sleep, circadian rhythm, hormones, obesity, hypertension and cardiovascular morbidity and mortality. All these are lifestyle related disorders.

**AGEING AND LOW BODY WEIGHT TYPE 2 DM** (LBW TYPE 2 DM)

Majority of the diabetic subjects in India are LBW type 2 DM. There are several publications on this subject. Indian College of Physicians published Indian data from several
centres in a technical series. The pathogenesis of this disorder is not clear. Some common elements of LBW type 2 DM and ageing are mentioned. These are (i) As age advances there is loss of lean tissue and increase in fat content. (ii) The blood glucose increases as the age advances. Our study and others have found a positive correlations between blood glucose and old age. (iii) It is also known that ageing can be delayed by low calorie diet (Calorie restriction is an important part of diabetes management). (iv) Stress aggravates ageing. It is to be noted that advanced glycation and products (AGE) in uncontrolled diabetic individuals gets deposited in various tissues of the body contributing to the development of complications, arteriosclerosis and ageing. Therefore LBW type 2 DM is possibly a result of premature ageing of beta cells and efforts to retard ageing may prevent DM.

**Pharmacological ‘U’ Turn**

Recently pharmacological interventions - use of acarbose in patients with impaired glucose tolerance has been suggested to delay the development of type 2 diabetes. Recently a study has shown that treatment with metformin in patients with impaired glucose tolerance has been to retard ageing may prevent DM.

There is a pressing need for primordial prevention in diabetes. The geographic distribution of population of India has a bearing in implementing the prevention programmes viz. the urban population group, urbanizing population group and rural population. Secondary and tertiary preventions are quite long distance placed ‘U’ turns.

The ‘U’ turn in Type 2 Diabetes Express Highway probably lies in lifestyle modifications - going back to traditional lifestyle with use of modern technology to achieve happiness. There is a difference between technology for comfort and technology for happiness. The latter must be the objective.

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**References**