REVIEW ARTICLE

Avoiding Type 2 Diabetes Express Highway from Infancy to Old Age – Focus on Newer Risk Factors

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Abstract

The chronicity and the long term consequences of Type 2 diabetes mellitus (T2DM) demands prevention of the disease. Recognition and correction of risk factors is therefore of prime importance. T2DM being a multifactorial disease, has several risk factors. Some newer risk factors have recently been identified viz. disorders in pregnancy, aberrations in breast feeding, sleep disorders, vitamin D deficiency and aging process. The present review gives a deeper insight into these risk factors which will help to avoid the T2DM express highway.

Introduction

Type 2 diabetes mellitus (T2DM) is a major non-communicable disease affecting millions of subjects across the globe. Its rising prevalence is a cause for concern. The disease has several adverse effects on body systems resulting in complications. T2DM results from both defects in both insulin secretion and insulin sensitivity and accounts for 90% of all diabetic cases. The World Health Organization estimated there were 135 million diabetic patients in 1995 and it is projected that this number will increase to 300 million in 2025.[1] Major contributions to the rise of diabetic patient population will be from India. This is probably a price we are paying for progress, urbanization and modern life style. In India, there has been a gradual transformation of villages to towns, towns to cities and cities to metros. Society is embracing modern life style. Hypertension, T2DM, sleep deprivation, sleep disorders like obstructive sleep apnea, ischemic heart disease are related to modern life style. Type 2 DM is a multifactorial disorder where genetics, nutrition, life style and sleep play important roles in its genesis. The Diabetes Prevention Programme (DPP)[2] demonstrated that intensive changes in life style (diet and exercise for 30 minutes /day five days a week) in individuals with impaired glucose tolerance prevented or delayed the development of T2DM by 58 % as compared to placebo. This signifies that other factors are operational which need to be identified and corrected. In India, the narrow diabetic lane in 1970, over a course of years, transformed into an express highway.[3] Several workers in India have documented this rise.[3] Insulin resistance is the core issue in T2DM and every effort must be made to improve insulin sensitivity.

Risk Factors for T2DM- established and newer

There are several established risk factors for the development of T2DM. These include 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 (B.P. ≥140/90mm Hg), low levels of HDLc(≤ 35 mg/dl) and/ or increased triglyceride levels (≥ 250 / dl) and polycystic ovary syndrome. Stress and sleep apnea as risk factors have been mentioned.[3]

The newer risk factors are 1. Sleep deprivation 2. Obstructive sleep apnea (OSA) 3. Breast feeding 4. Vitamin D deficiency 5. Aging.

Sleep Deprivation

Sleep deprivation is sweeping the globe. Sleep has important homeostatic functions. Individuals differ in their biological sleep need, but on an average the sleep duration of adults ranges from 7-9 hours. This can be seriously compromised by competitive life style which forces subjects to push sleep to a secondary level of importance. The entertainment sector is active 24/7 adding to the woes.

Chronic Partial Sleep deprivation is the most common form of sleep deprivation. The usual causes of sleep deprivation are not allowing enough time for sleep due to work pressures, school/college/coaching classes timings, sleep disorders, excessive worry, depression, repeated awakenings from noise eg bed partner who snores loudly. Disorders like diabetes, backache, cardiac failure, asthma also cause sleep disturbances. Watching late night television/mobile phones exposes the retina to bright light which can inhibit the release of melatonin and delay the sleep onset further. We have reported rebound sleep deprivation in elderly subjects due to late arrival of their loved ones from place of work.[4] Also sleep deprivation can be due to destroyed sleep architecture as seen in patients with sleep disorders viz obstructive sleep apnea(unconscious sleep deprivation).

Esther Donga et al[5] have reported that partial sleep deprivation during a single night induces insulin resistance in multiple metabolic pathways in healthy subjects. Also chronically reduced sleep times are associated with obesity.[6] Systemic inflammation has also been described in subjects with short sleep duration.[7] Sleep deprived subjects have tendency to overeat which promotes obesity. They can exhibit binge eating. Fast eating in

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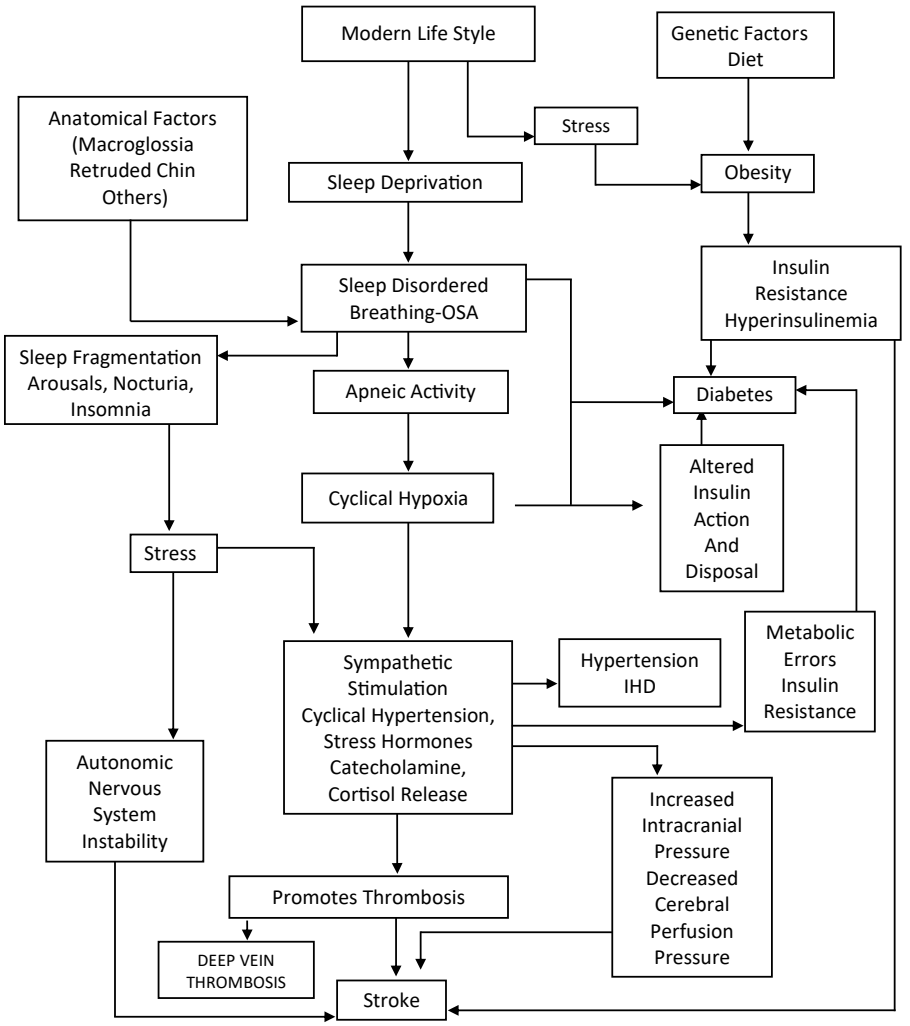

Flow Chart 1: Highlighting the path taken by nocturnal events in sleep disordered breathing- OSA culminating in cardiovascular, metabolic consequences and stroke

REM sleep deprived subjects has been reported by us.[8] Daytime sleepiness which occurs as a consequence of sleep deprivation can be overcome by consuming drinks(tea and coffee) and food. Sleepy subjects can chew tobacco and/ or smoke cigarettes, in soporific situations. Consumption of tobacco and smoking are also risk factors for T2DM. Sleep deprivation induces or aggravates snoring by increasing muscular hypotonia and delaying contractions of the dilator muscles of the pharynx.[9]

Sleep Disordered Breathing-Obstructive sleep apnea (OSA)

Sleep disordered breathing (SDB) is a spectrum of disorders consisting of snoring, upper airway resistance syndrome and sleep apnea. Sleep apnea can be obstructive, central or mixed.

Obstructive sleep apnea is a common disorder which often escapes clinical recognition due to poor awareness among health professionals and also in society. In OSA there is repetitive pharyngeal collapse in sleep resulting in cyclical hypoxemia, cyclical hypertension, release of stress hormones and catecholamines. Both these effects are known to decrease insulin sensitivity and worsen glucose tolerance (Flow chart 1).

Symptoms of OSA

Habitual snoring and excessive daytime sleepiness are two prominent symptoms of obstructive sleep apnea. Snoring can decline with aging (reduction the slow wave sleep). The other nocturnal symptoms include witnessed apneas, choking, dyspnea, restlessness, diaphoresis, acid reflux, drooling, somniloquy, frequent change of posture in sleep, bruxism and unable to sleep well. Insomnia can be a presenting symptom due to repeated arousals. The daytime symptoms include sleepiness, fatigue, morning headache, poor concentration, decrease libido or impotence, decreased attention, depression, decreased dexterity and personality changes. Mood swings and angry behavior is often present which may force the subject to seek psychiatric advice. Both OSA and diabetic subjects often experience postprandial drowsiness, poor concentration, fatigue and depression.

Risk factors

The risk factors for OSA include obesity, chronic sleep deprivation, alcohol, narrow upper airway. Upper airway abnormalities have been linked to breast feeding (see later).

OSA is a risk factor for several cardiometabolic disorders viz hypertension, ischemic heart disease, diabetes and stroke. Habitual snoring predicts the onset of diabetes.[10,11] Joq et al[12] have reported that frequent snoring is associated with reduced glucose tolerance, as assessed by abnormal oral glucose tolerance test (OGTT) results and higher levels of HbA1c. It is known that the most important risk factor for OSA is obesity in general and central obesity in particular. Both poor sleep quality (eg OSA patients) and quantity (eg sleep deprivation) have the potential to raise blood glucose levels due metabolic aberrations. Fasting levels may be higher than post lunch levels. A 2 hrs post glucose blood glucose estimation after consumption of 82.5 gms of glucose monohydrate will be necessary for patients, who show normal fasting and postprandial blood glucose levels, to detect impaired glucose tolerance.

Epidemiological data on OSA

The Sleep Heart Health Study reported that >10% of the general population has some degree of sleep disordered breathing, with daytime somnolence correlated to the breathing disorder severity.[13]

The Wisconsin cohort study was a population based study in which 602 working subjects aged 30 to 60 years were enrolled and studied with an overnight polysomnogram.In this cohort 24% of men and 9% of women had abnormal apnea hypopnea index (AHI) indices (>5 events per hour).[14]

Results from the Sleep Heart Health Study,[15] one of the largest community

Table 1: Comparison of type 2 diabetes mellitus and obstructive sleep apnea[18]

Particulars	Type 2 diabetes mellitus	Obstructive sleep apnea
Increasing prevalence with advancing age	Yes	Yes
Family history	Yes	Yes
Obesity	Often	Often
Lean subjects	Affected	Affected
Sleep disturbances	Often insomnia, excessive daytime sleepiness, early awakenings, may have associated OSA	Snoring + EDS, Sleep architecture disrupted. May have associated DM (OSA risk factor for DM)
Post-prandial drowsiness	Yes	Yes
Nocturia	Yes (Glycosuria)	Yes (Atrial natriuretic peptide release)
Metabolic syndrome	Part of metabolic syndrome	?A manifestation of metabolic syndrome. If associated with Syndrome X = Syndrome Z.

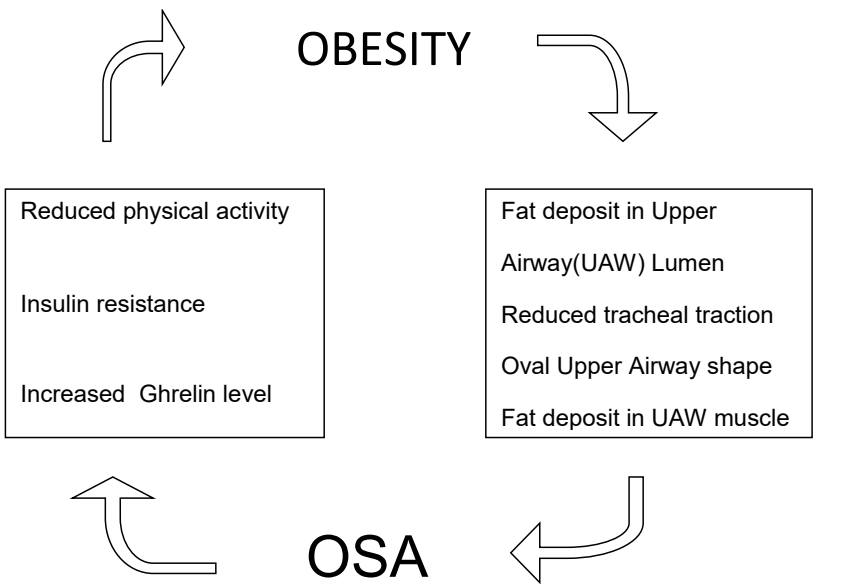

Fig. 1: Potential mechanisms formatting a vicious cycle where obesity may result in OSA and OSA may lead to weight gain[21]

based cohort studies with overnight polysomnography, indicate that OSA is associated with impaired fasting glucose, glucose intolerance and type 2 diabetes independent of confounding factors such as age, sex, race, waist circumference and BMI. Several studies show the prevalence of sleep disordered breathing increases with age ranging from 5% to 15% in middle aged adults to approximately 24% in community dwelling adults.[14,16]

OSA, Lean T2DM and Obese T2DM

Type 2 diabetes mellitus is an important constituent of metabolic syndrome both in the NCEP:ATP III and IDF criteria. However in developing countries majority of the diabetic patients are lean (60% non obese and many are lean BMI <18.5).[17] Although obesity is a major risk factor for OSA it can affect lean subjects due to anatomical factors on the face and upper airway viz macroglossia, retruded, small mouth. There are several similarities between Type 2 Diabetes Mellitus and OSA (Table 1).[18] Untreated OSA results in the gradual increase in body weight by several mechanisms. viz sleep deprivation, nocturnal cyclical hypoxia, sympathetic stimulation, disrupted metabolism and daytime tiredness and sleepiness. The development of insulin resistance as a consequence of OSA starts a chain reaction ultimately culminating into metabolic syndrome. OSA may be associated with changes in leptin, ghrelin and orexin levels leading to increased appetite. The other cause of increased appetite is REM sleep deficiency which is common in patients with OSA. Binge eating and fast eating are often exhibited by such patients. All these promote weight gain. We have observed metabolic abnormalities in lean OSA patients.[8] Lean metabolic syndrome has been mentioned.[18] Recent studies suggest that OSA may itself cause weight gain.[19,20] Further obesity aggravates OSA and a vicious circle is set up. It becomes difficult to assess whether obesity is a cause or consequence of OSA.(Chicken and egg story)[21] (Figure 1). Foster et al reported high prevalence of undiagnosed OSA (86.6%) among obese patients with type 2 diabetes.[22] Viswanathan et al reported high prevalence of OSA in T2DM patients.[23] Ip and associates observed an association between OSA and insulin resistance even in non obese subjects.[24] OSA occurring in lean young subjects can lead to insulin resistance (Flow Chart 1). This Insulin resistance paves the path for T2DM /metabolic syndrome. OSA patients have shown to have increased triglycerides, total cholesterol/high density lipoprotein (HDL) ratio and low density lipoproteins and lower HDL values.[25]

Recognition of OSA can at young age can be missed. The transitional phase from lean to obese is a very crucial. Proper sleep history from parents and relatives will often point to the presence of OSA since many years Childhood photographs would reveal a lean habitus. The clinical pointers of OSA at young age includes anatomical factors in upper airway, repeated upper respiratory infections, sleeping prone and somnambulism. Polysomnography is the gold standard for diagnosing OSA.

Pregnancy, Sleep Disordered Breathing (SDB) and Diabetes

Pregnancy is a diabetogenic state because the metabolic changes are accompanied by maternal insulin resistance. Pregnancy complicated by diabetes mellitus is associated with higher maternal and perinatal morbidity and mortality rates. During pregnancy majority of the women experience alterations in sleep. The physiological and biochemical changes of pregnancy places the women at risk for developing specific sleep disorders such as obstructive sleep apnea and restless leg syndrome. It must be appreciated that oxygen is also a nutrient to both mother and fetus. Pregnancy associated changes which increases the risk of sleep apnea include gestational weight gain, nasopharyngeal oedema, decreased functional reserve capacity and increased arousals from sleep. Factors which decrease the risk of sleep apnea include increased minute ventilation,

preference for lateral posture and decreased rapid eye movement sleep time. Snoring is commonly observed in pregnancy. Pregnant women possessing craniofacial abnormalities both in bony and soft tissues are believed to be predisposed to SDB. Schutte et al[26] observed that 27% of a group of normal women reported third trimester snoring. Weight gain and obesity are important risk factors for the development of SDB in pregnancy. Franklin et al[27] observed that habitual snorers gained more weight than did the non-snorers. SDB has been proposed as a risk factor for adverse maternal-fetal outcomes including pregnancy induced hypertension and small for gestational age births. Maternal hypoxia due to SDB-OSA has adverse effects on fetus causing fetal growth retardation.

Pregnancy induced hypertension increases the risk of adverse outcomes such as premature delivery, fetal growth retardation and maternal morbidity and mortality. Manju Aggarwal et al[28] reported maternal morbidity on terms of pre-eclampsia and meconium-stained liquor was higher amongst snorers and SDB population of pregnant subjects. Also a higher chance of IUGR and intra-partum asphyxia (Apgar Score <7) was noted in babies born to mothers having snoring during pregnancy. Approximately 28% of children born in India are of Low birth weight[29] LBW is associated with elevated glucocorticoid levels in later life. Also LBW with stunting and muscle wasting is followed by overweight and obesity in later life. All this contributes to insulin resistance. A story from the womb to the tomb.

Genetic Basis of OSA

Although obesity is the strongest risk factor for OSA and has a clear genetic basis, causal modeling suggests that only 35% of the genetic variance in the apnea hypopnea index(AHI) is shared with pathways that determine body weight. Thus the majority of genetic variance for the AHI is likely due to influence of genes that influence other pathways including those that influence craniofacial structure, ventilatory control and possibly sleep-wake patterns.[30]

Breast Feeding

Breast feeding is an integral part of infant growth. Craniofacial development is 90% complete by the age of 12 years.[31] Breast feeding has nutritional, immunological and emotional benefits. Also it is important for the development of swallowing action of the tongue, proper alignment of teeth and shaping of hard palate.[32] Breast has been designed to adapt to the shape of infant's mouth. The tongue movement of the infant while being fed is peristaltic underneath the breast. This is critical for proper development of swallowing, alignment of teeth and shaping of hard palate. The use of bottle feeding, pacifier use and infant habits such as excessive thumb sucking etc. can cause tongue thrusts and malocclusions. This may cause OSA. Skull research has shown that before the invention of modern baby bottle about 200 years ago people had minimal malocclusion or decay. Also high palates, overjets were rare.[33] Labbok et al[34] reported a direct relationship between length of breast feeding and occlusion; the longer the infant was breast fed the better was the occlusion. Further Kushida et al from Stanford described a formula for predicting OSA. It states that individuals with high palates, narrow dental arches, over jets, increased body weight and with large necks are at risk for OSA.[35] Therefore reduced duration of breast feeding favours the development of sleep disordered breathing which may manifest in young age paving the way for development of several consequences including type 2 diabetes mellitus. In India duration of lactation is advised for 24 months. However, maternal duties may restrict breast feeding.

Vitamin D

Vitamin D deficiency and diabetes have one major trait in common : both are pandemic. The role of vitamin D in several metabolic disorders is well known. There is increasing evidence that vitamin D acts as a modulator of immune system. There is strong link between vitamin D deficiency and type 1 and type 2 diabetes mellitus. There seems to be overall trend for an inverse correlation between levels of $1,25(OH)_2D$ and both disorders. Vitamin D deficiency has been associated with higher risks for metabolic syndrome and T2DM.[36] Population studies suggest that vitamin D and calcium may play a significant role in promoting beta cell function and insulin sensitivity. The National Health and Nutrition Examination Survey (NHANES), a large cross sectional study showed an inverse correlation between serum 25(OH) D and incidence of T2DM and insulin resistance.[37] Data suggest that T2DM patients with vitamin D insufficiency have increased C-Reactive protein, fibrinogen and Hb1AC compared with healthy controls.[38] This means that inflammation provoked by immune cells are implicated in insulin resistance and T2DM. Giulietti A et al[39] observed that administration of vitamin D ameliorates markers of systemic inflammation which are typically found in T2DM patients thereby possibly improving beta cell survival. Vitamin D3 supplementation of vitamin D-deficient type 2 DM patients tended to reduce insulin requirements and lower triglycerides.[40] Evidence also indicates that vitamin D treatment improves glucose tolerance and insulin resistance.

Aging

There is a complex interaction between aging, sleep and T2DM. Somatopause occurs early in adulthood between ages 25-35 years. This age range corresponds to the human life expectancy before the development of human civilization. People over the age of 65 years constitute more than 40 percent of cases of diagnosed diabetes.[41] It has been observed that blood glucose increases with advancing age.[42] Modern life style has generated several disorders including sleep disorders which have an adverse effect on aging. Also, changes in sleep patterns known to occur with aging bear a close relation to the progression of aging process. Further OSA results in oxidative stress which in turn aggravates ageing. Sleep can be the hidden agenda in the aging programme.[43]

With advancing age there is reduction of lean tissue and increase in fat content. The prevalence of sleep disordered breathing increases with age. Central obesity is a common feature of ageing process. The potential age dependent risk factors for development of sleep apnea in the elderly are increase in body weight, decreased lung capacity, increased upper airway collapsibility, increased sleep fragmentation, decreased slow wave sleep, decreased muscular endurance, decreased ventilatory control and decreased thyroid function. The potential age dependent outcomes

can be cardiovascular, metabolic and neurobehavioural morbidity. Therefore sleep apnea is an age dependent condition with other potential associated age dependent risk factors and outcomes.[44]

Parallels between aging and T2DM

Ageing can be retarded with low calorie diet. (Calorie restriction is an important tool in the management of diabetes.) Stress aggravates or can precipitate diabetes. Stress also aggravates aging. Lastly diabetes itself aggravates ageing via deposition of advanced glycation end products in various tissues of the body. Type 2 diabetes mellitus is possibly a state of premature aging.[3]

Continuous Positive Airway Pressure and T2DM

Treatment of obstructive sleep apnea/hypopnea syndrome (OSAHS) in patients who also have diabetes with CPAP decreases the insulin requirements.[45] In a well designed study improvement in insulin sensitivity by CPAP therapy in patients with OSA has been demonstrated by Harsch et al.[46] Forty patients of OSA were taken up in this study. Lindberg et al[47] demonstrated reductions in fasting insulin levels and insulin resistance(estimated by HOMA) after 3 weeks of CPAP treatment in 28 men with OSA compared with matched controls. We have also reported beneficial effects of CPAP in 4 patients with type 2 diabetes.[48] This has important implications since patients with impaired glucose tolerance and mild diabetes can look forward to reversal of diabetes with treatment of associated OSAHS.

Conclusions

Recognition and correction of risk factors both old and new are of paramount importance to avoid the T2DM express highway. Prevalence studies indicate that sleep deprivation and OSA are highly prevalent. Sleep consultation and management of sleep disorders is gaining ground in the prevention of T2DM. OSA treated with continuous positive airway pressure improves insulin sensitivity and therefore prevents progressive beta cell failure. Detection of OSA in pregnancy is important. Optimal breast feeding is advisable. Vitamin D status needs to be checked. Efforts to retard aging process are essential.

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