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Review Article

A REVIEW ON IMPLICATIONS OF BIOLOGICAL RHYTHMS ON LONG-HAUL TRAVELLERS IN DIFFERENT TIME ZONES AND SEDENTARY LIFESTYLE: WORSENING OF DIABETES MELLITUS

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ABSTRACT

Incidences of Diabetes mellitus (DM) gets worsen on frequent long-haul travel in different time zones and sedentary lifestyle. An extensive review of the published articles related to diabetes, the effect of lifestyle modification (exercise and diet) and travelling of diabetic people across different time zones were done and these were accessed from Pubmed-Medline, Web of Science, Cochrane Library, EMBASE, Lancet and Diabetes Care. The study done by different scientists were compared and interpreted for the worsening of cases of DM. For long-haul travel in different time zones, it was observed that, due to metabolic disturbances, serious consequences of DM were observed in flight, but that can be prevented if pre-advice are taken by the patients and strictly followed. The cumulative incidences of diabetes of 10 cases were compared and mean cumulative incidences of control group (following sedentary lifestyle) was 42.77% and of intervention group (following healthy diet and moderate physical activity) was 22.11% confirming that implementation of the healthy diet and exercise as regular physical activity caused the lowering of cumulative incidences of diabetes. According to the research conducted on frequent flyers and sedentary lifestyle, the hypothesis quoted by various scientists is that DM is a metabolic disorder which easily gets affected by the frequent changes in the metabolism leading to its high incidences. Thus, the concept of chronobiology comes into light that requires more research to correlate the disturbed biological rhythm (Circadian cycle) to the incidences and severity of DM condition (worsening or increased incidences of DM).

Keywords Circadian rhythm, Chronobiology, Chronopharmacology, Diabetes Mellitus, Jet-lag, Long-haul travel, Sedentary lifestyle.

INTRODUCTION

Overview of Diabetes Mellitus with Diagnostic Criteria

Diabetes mellitus (DM) was reported in the Egyptian manuscript about 3000 years ago and, most probably it is among the oldest known diseases to man[1]. DM is a metabolic disorder characterised by the presence of chronic hyperglycaemia and glucose intolerance caused due to a defect in insulin production, insulin action or both. Insulin as a hormone induces conversion of carbohydrate into energy. The chronic hyperglycaemia is accompanied by the impairment in the metabolism of carbohydrate, lipids and proteins[1-4]. DM is broadly classified into two main categories: type I (an autoimmune disease of younger patients in which there is a lack or defect in insulin production causing hyperglycaemia) and type 2 (a metabolic disorder that results from the inability of insulin production from the body or defect in proper utilisation of the insulin produced leads to hyperglycaemia[5]. In DM, metabolic disturbances and chronic hyperglycaemia cause long-term tissue and organ, damage and dysfunction leading to conditions like Diabetes Retinopathy, Diabetes Nephropathy and Diabetes Neuropathy[6]. When DM is not cured well, its risk of complications increases which ultimately cause the increase in its treatment cost. Treatment not only requires the cost of medicine but also changes in their daily activities i.e. in lifestyle causing social, psychological, emotional as well as psycho-social problems as one has to bring a lot of changes in their habits or in daily activities. International Diabetes Federation (IDF) reported that in 2011, there were 356 million diabetic people in the world and was estimated that it would increase to 552 million people by 2030, thus in the 21st century, it is considered as one of the most challenging health problems[7]. Considering the prevalence of DM in India, it is reported that in 2000, the prevalence of patients with DM was 31 million in India which are expected to reach 79 Million by 2030[8].

There is various research done to identify the diagnostic criteria for the patients with non-diabetes, pre-diabetes and diabetes condition. Various assessment parameters that define the diagnostic criteria of DM basically include the blood test that reports the pre-diabetes and diabetic condition. Various assessment terms coined include Casual plasma glucose concentration (CPGC), Fasting plasma glucose concentration (FPGC), Oral glucose tolerance test (OGTT), Postprandial blood glucose test, Glycated haemoglobin and Fructosamine test.

CPGC value less than 200mg/dl indicates non-diabetic condition whereas its value greater than or equal to 200mg/dl is the indication of the diabetic condition. The word "Casual" in the CPGC parameter describes the time of the day irrespective of the last meal time. CPGC value indicates diabetes condition but it has to be reconfirmed by other parameters. FPGC value elucidates the non-diabetic, pre-diabetic, and diabetic condition. Values being less than 100mg/dl is indicative of the non-diabetic condition, 100-125mg/dl of the pre-diabetic condition and greater than equal to 126mg/dl on at least two tests fasting glucose clarify the diabetic condition."Fasting" word in the parameter FPGC means no caloric intake for at least 8 hours. An abnormal result of the test must be repeated on a different day.

As described by the WHO, during the OGTT by using a 75-g glucose challenge, the two-hour plasma glucose greater than or equal to 200 mg/dl conclude the diabetic condition whereas pre-diabetes is diagnosed if the two-hour blood glucose level is 140–199 mg/dl. When the value of the CPGC is 160-200mg/dl and FPGC value is 110-125mg/dl, then OGTT test is conducted. Postprandial Blood Glucose Test indicates the diabetic condition if the blood glucose value after 2 hours of the meal is measured and found to be equal to or more than 200 mg/dl. Glycated haemoglobin (HbA1c) measurement is also a retrospective indicator of the average glucose level in an individual. HbA1c>=6.5% value indicates the diabetic condition in an individual. Fructosamine test is not used as the screening test whereas it is conducted to keep the close check over the glucose level. It measures glycated albumin and thus can also serve as a marker to monitor the blood glucose level. Glycated albumin is taken over a period of 1 to 3 weeks, reference interval being 205-285 micromol/L[1,9].

Assessment parameters of diagnostic criteria of DM are illustrated in Table 1.

Figure 1 illustrates the comparative view of the estimated worldwide prevalence of diabetes in the adult population in 2017 and 2045.

Understanding Body Rhythms and Chronobiology

In a certain diseased state, the physiological functions of the body depend upon the body rhythms[9]. Rhythms are present in prokaryotic to eukaryotic plants and animals to higher vertebrates including humans. The biological rhythms can be characterised into different types on the basis of the duration of each cycle, which are:

- Circadian rhythm: A rhythm of approximately 24 hours like the sleep/wake cycle.
- Infradian rhythm: A rhythm with a frequency of less than one cycle in 28 hours like the oestrous cycle.
- Ultradian rhythm: A rhythm with the period of fewer than 20 hours like pulsatile episodic secretion of hormones.
- Circaseptan rhythm: A rhythm with the period of a week.
- Circamensual rhythm: A rhythm with the period of about a month, like the human menstrual cycle.
- Circannual rhythm: A rhythm with the period of about a year i.e. 365.25 days. Ex: reproductive rhythms in some animals follow the circannual rhythm.
- Diurnal rhythm: This rhythm is the extension of the circadian rhythm but one must be in synchrony with the day and night cycle.

'Zeitgeber' provides with information on the periodicity of the environmental variables to the organisms. Thus it can be defined as those cyclic environmental cues that can entrain free running, endogenous rhythms[10].

The branch of science dealing with the biological rhythm in a living organism is known as Chronobiology. As per the studies are done, basically there are three disciplines that account for the influence of biological rhythms, namely: Chronophysiology, Chronopathology and Chronopharmacology. The branch of Chronobiology that deals with the pharmacological aspects i.e. the effect of drugs on the biological rhythm and relation of the biological rhythm and, endogenous periodicities to the effect of drugs is known as Chronopharmacology[9,11]. Chronopharmacology is further subdivided into chronotherapeutics, chronokinetic, chronergy, chronesthesy, chronotoxicology.

- Chronotherapeutics: It deals with the knowledge of biological rhythms exacerbates with the kinetics, efficacy and safety of medications by proportioning their concentrations in synchrony with 24 hours of the rhythms of determinants of disease.
- Chronokinetic: It deals with the study of temporary changes in absorption (A), distribution (D), metabolism (M), excretion (E) and the effect of time changes on these processes.
- Chronergy: It basically deals with the differences of biological rhythms on the effects of drugs.
- Chronesthesy: It deals with susceptibility or sensitivity of the target system of the drugs due to changes in biological rhythms.
- Chronotoxicology: It can be considered as an aspect of chronodynamics that refers to the dosing time of the medications such that the impact of differences in biological rhythms on the severity of diseases[11-12].

The hypothalamus of the brain controls various physiological processes like sleep/wake cycle, sexual behaviour and reproduction and rhythms of insulin secretion and metabolic control such as glucose metabolism, lipid metabolism. All these functions follow circadian rhythms[13]. Circadian rhythms of the physiological functions of the body are controlled endogenously by the circadian clock which resides in the Suprachiasmatic Nucleus (SCN) of the anterior hypothalamus which is entrained directly by the light[11,14,17]. Disturbance in the sleep/wake cycle is likely to be associated with the development of metabolic diseases[14-15]. The first evidence that showed that SCN is involved in daily rhythm in the glucose metabolism came from the work of Nagai and Nakagawa, who showed that lesions in SCN abolish the daily rhythms in plasma concentrations of glucose and insulin and confirmed the existence of pronounced differences in day/night in response to 2-deoxyglucose (a glucose utilisation inhibitor)[13].

Clock Genes and Cellular Metabolism

The mechanism that governs the circadian rhythmicity involves complex procedure of gene expression. At the cellular level, biological rhythms depend upon the activity of the molecular clock which is an autoregulatory feedback loop of transcription factors known as clock genes. Regulators of transcription factors includes circadian locomotor output cycles kaput (CLOCK), brain and muscle aryl hydrocarbon receptor nuclear translocator-like protein-1 (BMAL1, also known as ARNTL1), period circadian protein (PER1, PER 2, PER 3), cryptochrome (CRY1 and CRY 2), and the nuclear receptors retinoic acid receptor-like orphan receptor alpha (RORα) and reverse thyroid receptor α (REV-ERBα). CLOCK and BMAL1 form a complex that drives PER, CRY, REV-ERBα and RORα transcription. The protein products of the PER and CRY genes heterodimerise to form PER–CRY and repress BMAL1–CLOCK activity. REV-ERBα and RORα are involved in providing the additional stability to the molecular oscillator as they synergistically control the timing and amplitude of the expression of BMAL1. A rhythmic post-translational modification of clock proteins, including phosphorylation of the PER–CRY complex, introduces temporal delays that contribute to the 24 h period of the clock. Considering at the cellular level, in metabolism condition, the CLOCK and circadian rhythms influence each other; daily variations in glucose uptake and metabolism influence the clock through metabolic sensors, such as adenosine monophosphate-activated protein kinase (AMPK). Further, REV-ERBα is activated by haem, levels of which vary greatly in response to nutrient availability[13,15,17].

Melatonin, Circadian Rhythms and DM

In the brain, SCN receives zeitgebers from the retina and respond by coordinating the activity of the central system with the peripheral system with the help of endogenous signalling mechanisms, glucocorticoids and melatonin. Melatonin is known as the hormone of darkness and its plasma concentration during the night ranges from 80-100 pg/mL to low levels 10-20 pg/mL during the day. Melatonin is secreted by pinealocytes during the night in both diurnal and nocturnal mammals. It binds on melatonin receptor and due to its phosphorylating activity, regulates the expression of genes involved to maintain circadian rhythm. It influences the secretory activity of pancreatic islets cells, metabolism of glucose in the liver, and insulin sensitivity at target tissues. Thus it can be reasonably hypothesised that the altered level of melatonin may impact on the development and severity of metabolic disturbances in patients of type 2 diabetes[5,15]. As per the evidence from the clinical study of circadian disruption in controlled- laboratory conditions projected that exposure to misalignment, as occurs in chronic jet lag or shift work, leads to conditions like hyperinsulinaemia, hyperleptinaemia and misaligned cortisol rhythms. It was reported that only 4-5 days of misalignment can produce a significant increase in 2h postprandial glucose. As per author, half of the participants were categorised as prediabetic during misalignment (Plasma glucose > 8.06 mmol/l)[16]. If we consider at the cellular level, then, melatonin exerts its effect through melatonin receptors of peripheral tissues, thus maintaining the circadian rhythm. Similarly, other physiological processes such as glucose metabolism are regulated by circadian system[5].

Jet Lag and Circadian Rhythms and DM

Due to globalisation, travelling by plane has become an essential part of the transportation for an individual for business, education, tourism and others but it is unfortunate that people are negatively affected by the long-haul travel in different time zones or intercontinental travel in several ways including jet lag. ”Jet lag is a syndrome caused by disruption of ‘body clock’ and affects most air traveller crossing five or more time zones; it is worse on eastward than on westward flights”. It is caused due to the temporary differences between the environmental sufficient sleep/wake cycle and its endogenous cycle generated by the circadian timing mechanism. The circadian clock provides with the information pertaining to sunlight and darkness and causes physiological disruption if it does not reset quickly. It can affect all age groups but older people present more severe symptoms. More the number of time zones crossed, more are the pronounced symptoms[8,10]. Modification in lifestyle such as nocturnality, intake of excessively rich diets causes the disturbance in sleep/wake cycle along with other circadian rhythms. Long-haul travel crossing different time zones make an individual prone to the disturbance in circadian rhythms. Thus the deviation in circadian patterns favours the occurrence of DM[5]. In long-haul travel, in recent times, guidance to patients involve general precautions to be taken regarding diet and medication and the impact of jet lag causes adherence to medication during travelling and thus maintaining blood glucose level and metabolic regulation[25].

Lifestyle and DM

In modern civilisation, the most prevalent problems in the healthcare sector are the numerous complications caused by DM, which can be effectively controlled by lifestyle modification i.e. non-pharmacological treatment must also be emphasised to control incidences and prevalence of DM. Recognition of the lifestyle factors which are responsible for the increscent number of people suffering from DM and its complications in recent years may lead to the development of strategies that can decrease the number of new cases. It is a general belief that an energy-dense western style diet in conjunction with the sedentary lifestyle is the major cause of the development of type 2 DM (T2DM). Essentially it is required that alteration or modification in one’s lifestyle can prevent the risk of DM and its complications. Lifestyle management is an effective way of managing DM with the less adverse effect which is mandatory for managing the disease. Poor physical fitness and dietary patterns increase insulin resistance and promote hyperglycaemia. WHO has recognised the importance of dietary patterns in DM patients and thus healthy diet include around 45% carbohydrate intake and lesser fat, protein and cholesterol intake. Exercise training programs influences and manages DM especially T2DM. The mechanism that is involved, is the increase of glucose uptake via glucose transporter 4 (GLUT4) to the skeletal muscle during the exercise which is responsible for reducing blood sugar level in T2DM patients. It is specifically the aerobic exercise that improves the physiological parameters, including glycaemic control, fasting blood glucose level and lipid profile. It is clear that the implementation of lifestyle modification potentially decreases the associated morbidity and mortality related to DM. Regular exercise, healthy dietary plans and controlling the weight through health education programs must be given priority for betterment in individual’s health. Addition to this, self-monitoring and assessment is also required for regular follow check up. This overall needs the family support and emotions in managing the therapeutic regimen of DM[18-24].

Search Engines Used

An extensive review of the published articles on the introduction of DM, the effect of sedentary lifestyle (exercise and diet) and frequent flying of diabetes patients across different time zones were done and accessed from Pubmed-Medline, Web of Science, Cochrane Library, EMBASE, Lancet, and Diabetes Care. The literature reviewed covered more than thirty published articles focusing on diabetes and its diagnostic criteria and the incidences and condition of diabetes patient on travelling in different time zones and following modification in their sedentary lifestyle.

Impact of Frequent Traveling in Different Time Zones

Due to globalisation, increscent numbers of people are travelling in flight; individuals have become more prone to frequent flying and crossing different time zones. During travel, the individual’s meal content and time vary that can lead to metabolic dysregulation in DM patients. In the study, we have included only patients suffering from DM and the problems faced by them during and after travel. The main concern was on the effect on glucose level and metabolic regulation of the patient. Very few studies are done to study the impact of frequent travelling in different time zones on the condition of DM patients. Three studies, published in authorised journals were reviewed to study the glucose level and metabolic regulation during travel.

Study of Driessen et al[26] was done to check whether there is any clinically significant problem in DM patients during travel in specifically tropical countries. Young and old patients ranging from 26-74 years of age of patients participated in the study by the telephonic interview who had already received pre-travel advice at the travel clinic of the Academic Medical Centre, Amsterdam. Data from the patients were collected on medical problems related to insulin-dependent DM (hypo-/hyperglycaemias, infectious complications, practical difficulties, exploring risk factors) and general health problems. Metabolic dysregulation and poor glycaemic control were reported along with the occurrence of secondary symptoms like fever. Of all the patients included in the study, 68% reported metabolic dysregulation and 36% reported high blood glucose level. In this study, symptoms of fever were reported to be an important cause of hyperglycaemic dysregulation with difficulties in adjusting the insulin dose to the increased blood glucose levels. Fever with or without diarrhoea can result in an increase in counter-regulatory hormones that raise blood glucose, possibly leading to diabetic ketoacidosis. In this study, the author concluded that as the number of diabetic travellers to the tropics will rise, an increase in morbidity and mortality abroad can be expected in the near future. The data of this study indicate that the further research is necessary. Incidences of glycaemic dysregulation among diabetic travellers should be assessed and compared with the non-travelling diabetics.

Shraga et al[27] conducted the study in young adults to evaluate the rate and characteristics of travel associated health risks among young adult travellers with type 1 DM. There were no significant differences observed between the individuals with and without DM regarding the total number of trips, number of trips per person, length of trips and the purpose of trips. Structured questionnaires were used to access information from young travellers with mean±SD ages of the diabetic and control group were 26.6±5.0 and 26.9±2.6 years respectively regarding their 154 international trips that lasted for 7 days or more on last 5 years. No DM patients sought medical attention with acute health problems. The data were analysed as per the number of trips and separately for trips to developing countries and those to developed countries. It was reported that prior to 71% of the trips to developing countries, individuals consulted their physician. It was reported in the study that in 90% of all trips, individuals informed their companions that suffer from DM and this is very essential for management of severe hypoglycaemia during travel. In the study, 55% of the patients reported worse glucose control while travelling than during the preceding period whereas only 7% of all trips reported to have poor metabolic control. We can conclude from the study that the young travellers with diabetes do not seem to be at increased risk for travel-related diseases or worsening of the condition in comparison to healthy individuals but this conclusion was applied to only to young individuals who routinely maintain a very good metabolic control.

Another study that was reviewed was of the Burnett JCD[28] who conducted the study in patients with 45-50 years with the aim to determine what problems are faced by the patients with DM during air- travel who is under the insulin usage medication. Census study by self-administered questionnaire of patients with DM was done. In this study, the author split those returning questionnaires into four groups as respondents of long-haul travel, short-haul travel, seldom travelled and never travelled. Hypoglycaemia was reported to affect 10.2% of all travellers and out of those experiencing hypoglycaemia symptoms, 31% had severe symptoms requiring help. As this study was conducted in Aberdeen, which is the centre of the UK oil industry and the clinic staff of there was aware of the need to raise the issue of travel advice with patients. Almost 99% of patients using insulin had no problem during flight abroad. It was concluded that the written patient education information and pre-advice from the general practitioner can successfully help the patients in seeking no or lesser metabolic dysregulation and hypoglycaemia issues during travel, thus reducing the worsening of the condition of DM patients.

A comparative study was done of these three studies and tabulated in Table 2.
Graphical representations are done of studies comparing the metabolic disturbances and glucose level variation in figure 2.
Figure 3 illustrates the Burnett JCD study for the percentage of patients suffering from serious consequences due to long-haul travel in different time zones

Impact of Lifestyle Modification (Exercise and Diet) on DM

Lifestyle factors that risk the DM condition and incidences include the diet poor in fibre, plant food in general (relative risk increase by 44% to three-fold), regular consumption of sugar-sweetened beverages (relative risk increase by 20–30% compared to non-consumption) little physical activity (leisure time/occupational) (relative risk approximately 40% higher compared to high total physical activity), prolonged TV and monitor viewing/sedentary time (relative risk increased by approximately 3% per hour television watching), exposure to road traffic (noise, fine particulate matter) (relative risk increased by 20–40% for exposure to 10 dB higher noise level), smoking (relative risk increased by approximately 30%/60% for light/heavy smokers), short sleep duration and poor quality (relative risk increased by approximately 9% for every hour of shorter sleep duration), low mood/stress/depression (relative risk increase highly variable, depending on the definition of stress and depression) Low socioeconomic position (relative risk increased by 40–100% when compared to high socioeconomic level). These all factors are significantly associated with the body mass index (BMI) of an individual. Numerous papers published in authorised journals were reviewed for the study of the intervention of exercise and diet on the incidences of DM condition.

The studies were reviewed to check the incidences of DM. Cumulative incidence of DM is higher in the control group compared to the intervention group. The cumulative incidences of DM in the intervention group and in control was found to be respectively, Knowler et al[30] 14.4% and 28.9%, Kosaka et al[32] 3.0% and 9.3% , Lindstrom et al[31] 9% and 20% , Penn et al[35] 55% less in intervention group as compared to control group, Ramchandran et al al[33] 39.3% and 55% , Roumen et al[34] 18% and 38%, Saito et al[37] 12.2% and 16.6%, Xu et al[38] 14.6% and 17.5%, Walker et al[36] reported to reduce the incidence of diabetes by 28-59% and Pan XR[29] 46.0% and 67.7%.
Tabulation of all these 10 studies is presented in table 3.

Figure 4 clearly shows the cumulative incidences of DM after the implementation of modification in lifestyle.

Table 1: Scale for measurement of Diabetes mellitus condition

S.No.	Assessment Parameter	Diagnostic Value	Conclusion	Diagnostic Value	Conclusion
1	Casual Plasma Glucose Concentration(CPGC)	<200mg/dl	Non Diabetic	>=200mg/dl	Diabetic
2	Fasting Plasma Glucose Concentration(FPGC)	<100mg/dl	Non Diabetic	>=126mg/dl	Diabetic
		100-125 mg/dl	Prediabetes		
3	Oral Glucose Tolerance Test(OGTT)	140-199 mg/dl	Prediabetes	>=200mg/dl	Diabetic
4	Postprandial Blood Glucose Test	<200mg/dl	Non Diabetic	>200mg/dl	Diabetic
5	Glycated Haemoglobin (HbA1c)	<=6.5%	Non Diabetic	>=6.5%	Diabetic

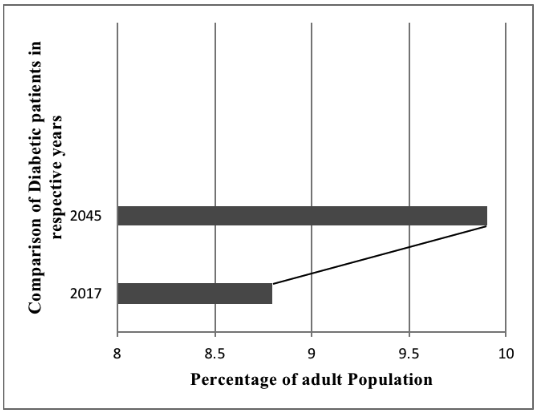

Figure 1: Comparative view of estimated worldwide Diabetics prevalence in the adult population in 2017 and 2045.
In 2017, 8.8% of the adult population worldwide had diabetes whereas estimation was done that in 2045, 9.9% of the adult population worldwide will have diabetes. (This report was generated by Statista Report worldwide)

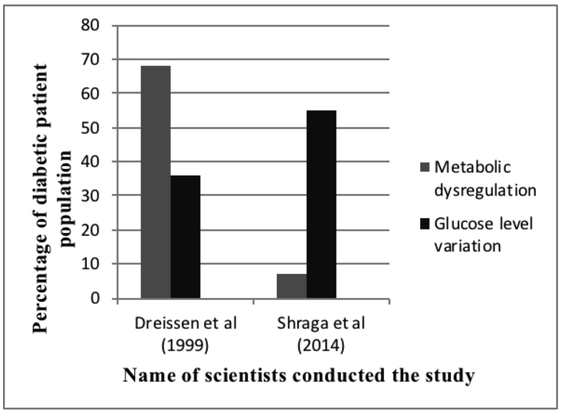

Figure 2: Comparative study of two scientists on the condition of diabetic patients in long-haul travel
Two parameters namely, metabolic dysregulation and glucose level variation were studied to check the worsening of the conditions of the diabetic patient population

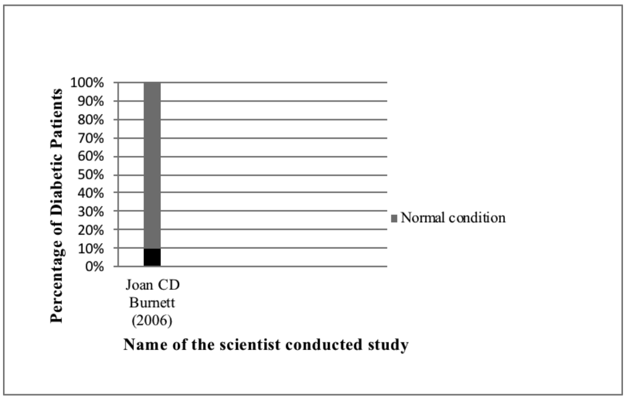

Figure 3: Study of Joan CD Burnett (2006) for the serious consequences of diabetic patients in long-haul travel.
In the study conducted by Burnett JCD (2006), it was observed that, out of all DM patients, only 10% suffered from serious consequences during travel while 90% were normal.

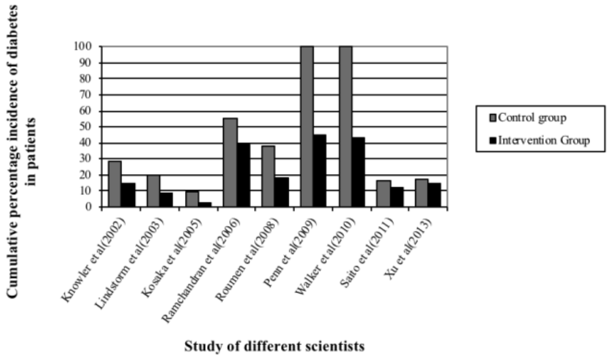

Figure 4: Comparative study of scientists in different years for the cumulative incidence of diabetes in patients after lifestyle modification (Exercise and diet)
Control group included diabetic people following sedentary lifestyle i.e. no check on the diet plan or physical exercise. Intervention group included diabetic following modified lifestyle i.e. including healthy protein rich diet and moderate physical activity as per the scientists study in respective years.

Table 2: Comparative study of diabetic incidence during travel

Name of Scientist	Country	Study area	Number of patients	Mean age of patients	Design of study	Observation	Conclusion	Inference
Driessen et al[26] (2006)	Netherland	Travel Clinic of the Academic Medical Centre, Amsterdam	9385 out of which 19 reached the interview	26-74 years	Retrospective, descriptive, cohort study. Telephonic interview by questionnaire	Out of 19 respondent,68% showed metabolic dysregulation and 36% had a high glucose level.5 patients in the study showed difficulty in adjustment of dosage of insulin	Metabolic dysregulation was clinically significant. Secondary symptoms like fever were also noted which showed serious health problems	During travel, maintenance of insulin dosage and metabolic control was difficult for the adult and old age patients.
Burnett JCD[27] (2006)	U.K	Grampian Diabetes Centre, Woolmanhill Hospital, Aberdeen	1329 patients, out of which 493 patients completed the questionnaires	45-50 years	Census study by self-administered questionnaires .	Hypoglycaemia affected 10.2%of total travellers.	There was no serious problem during travelling as they were well advised for the insulin usage in different time zones.	Advice from the general practitioner before travelling caused no serious consequences.
Shraga et al[28] (2014)	Israel	Pediatric Endocrinology and Diabetes Unit of Safra Children's Hospital, Juvenile Diabetes Centre of Maccabi Health Care Services	48 each in the diabetic group and in the control group	18-32 years	Retrospective, structured questionnaire	Only 7% of all trips reported poor metabolic control.55% of the total patients reported worse glucose control while travelling than the preceding period but it was managed without causing serious consequences	It was concluded that young travellers don't have serious travel-related issues as compared to healthy individuals of their age. It was for the patients who routinely maintain good metabolic control.	In young travellers during travel, maintenance of metabolic control and thus insulin dosage was not difficult. Thus they don't report to have travel related issues compared to the healthy individual of the same age

Table 3: Study of diabetic incidence after lifestyle modification

Scientist conducting study	Country	Study area	Sample Size	Lifestyle Characteristics		Observation	Conclusion	Inference
				Exercise	Diet			
Pan XR et al[29] (1997)	China	Health care clinics in Da Qing city in the Hei Long province in the northern part of China	577	Exercise recommended depended on age, past exercise patterns, and the existence of health problems other than IGT. The exercise included slow walking, faster, cycling, ballroom dancing (slow) Slow running, and games like volleyball, jumping	Diet containing 25-30 kcal/kg body weight 55-65% carbohydrate, 10-15% protein, and 25-30% fat. More vegetables, control their intake of alcohol and reduce their intake of simple sugars.	Cumulative incidence of diabetes was 46.0% for the intervention group and 67.7% for the control group	Diabetic incidence was found higher in the control group as compared to the intervention group	Six-year intervention has resulted in a delay of the onset of diabetes and caused lower incidences of diabetes.
Knowler et al[30] (2002)	USA	27 medical centres	3234	Achieve moderate activity exercise for 150 minutes in a week	Low calorie or low-fat diet	Cumulative incidence of diabetes was 14.4% for the intervention group and 28.9% for the control group	Diabetic incidence was found higher in the control group as compared to the intervention group	Moderate exercise and a low-fat diet reduced the incidence of diabetes
Lindstrom et al[31] (2003)	Finland	Helsnki, Kuopia, Turku, Tampere and Oulu health centre	522	Endurance and Resistance training	Recommended weight loss of 0.5-1 kg per week	Cumulative incidence of diabetes was 9% in the intervention group and 20% in the control group	Diabetic incidence was found higher in the control group as compared to the intervention group	Maintaining the weight and practice of endurance and resistance training improves the condition of patient causing reduction in diabetes incidence
Kosaka et al[32] (2005)	Japan	Toranomon Hospital	458 (only males)	Achieve and maintain moderate activity exercise eg:30-40 minutes of walk daily	Advised for food alternatives and thus maintained the BMI of 22	Cumulative incidence of diabetes for the intervention group and control was 3.0% and 9.3% respectively. Additionally, it was noted that at the end of 4 years of study, improvement in OGTT level was also noticed as 53.8% in intervention group and 33.9% in the control group.	Diabetic incidence was found higher in the control group as compared to the intervention group	Moderate activity exercises and food diet additives maintaining the BMI caused the reduction in diabetes incidence
Ramchandran et al[33] (2006)	India	Various service organizations	531	Everyday 30 minutes brisk walking	Advised on healthy food intake	Cumulative incidence of diabetes was 39.3% for the intervention group and 55% for the control group	Diabetic incidence was found higher in the control group as compared to the intervention group	Healthy food intake and simple brisk walking caused the reduction in the diabetic incidence

Roumen et al[34] (2008)	Netherlands	Maastricht, Netherlands	147	Per day 30 min, 5 days a week and 3 times participation in activity wearing a heartbeat watch	5-7% weight loss. Healthy diet advised	Cumulative incidence of diabetes was 18% for the intervention group and 38% for the control group	Diabetic incidence was found higher in the control group as compared to the intervention group	Follow up of the healthy diet and physical activity concluded the reduced diabetic incidence
Penn et al[35] (2009)	England	Royal Victoria Infirmary Newcastle upon Tyne	102	Physical activity equivalent to 30minute and moderate activity everyday	Achieve BMI of 25 so low fat and increased energy from carbohydrate	Cumulative incidence of diabetes was found to be 55% less in the intervention group as compared to the control group	Diabetic incidence was found higher in the control group as compared to the intervention group	Moderate physical activity and low-fat diet reduced the incidence of diabetes
Walker et al[36] (2010)	Australia	A systematic literature search was undertaken of Medline, EMBASE, the Cochrane Library and the Cumulative Index.	4864 patients. Four cohort studies were done	Regular exercise with the additional expenditure of 2000Kcal $week^{-1}$	Low-fat, High protein diet	The incidence of diabetes was reduced by 28-59% in the intervention group	Diabetes Incidence was reduced in the intervention group	Regular exercise and maintenance of a healthy diet consisting of low fat and high protein diet cause a reduction in the incidence of diabetes.
Saito et al[37] (2011)	Japan	38 Hospitals and clinic across Japan	641	Pedometers with 70,000 steps per week	5% weight loss. Maintenance of fat and carbohydrate intake. Self-goal to achieve a healthy diet	Cumulative incidence of diabetes was 12.2% for the intervention group and 16.6% for the control group	Diabetic incidence was found higher in the control group as compared to the intervention group	Healthy carbohydrate food intake and recommended pedometers proved to have decreased diabetic condition incidence
Xu et al[38] (2013)	China	2 Health centres in urban areas of Shangai	88	Moderate activity like 30-40 minutes of walk daily	For the first 3 months breakfast replaced with low glycaemic index food. Healthy food advised	Cumulative incidence of diabetes was 14.6% for the intervention group and 17.5% for the control group	Diabetic incidence was found higher in the control group as compared to the intervention group	Moderate physical activity and low glycaemic diet has consequences of the low incidence of diabetes

DISCUSSION

In this era of modernisation and globalisation, people are more prone to travel by air crossing different time zones and adaptation of sedentary lifestyle. The travelling by air are higher in recent times due to the tendency of individuals for the luxury and time saving, and the travelling may be due to any reason for it be business, sport, tour, holiday and academic. Patients with DM are also in increscent number in travelling and sedentary lifestyle. The study compares the impact of frequent travelling by the DM patients on parameters consisting of metabolic regulation, glucose level and development of secondary symptoms such as fever. Not very much research has been done on the impact of travelling in different time zones. Various articles published in authorised journals provide the management of DM "up in the air". The studies were reviewed and 3 studies are included that provide with different assessment parameters for the condition of patients. Studies included Driessen et al[26] study that was conducted in the year 1999, Burnett JCD[28] study in the year 2006 and the study of Shraga et al[27] done in 2014. These studies focussed on the severity of patients during travelling compared with the normal people without DM. Also focussed the problems faced by them in metabolic regulation, glycaemic control and management of the use and timing of insulin dosage, those who were dependant on insulin pumps. The main issue with the insulin usage in long-haul travel crossing different time zones was its storage in the flight in the appropriate temperature and humidity and its timing of medication which may vary due to different time zones. These studies also focussed on the worsening and severity of the disease as per age group. Old people with DM tend to suffer more complications than young adult travellers. Pre-advice from the general practitioner or from the travel clinic provided fewer incidences of the severity of disease and are less prone to metabolic and glucose level disturbances.

The sedentary lifestyle is also the key factor for the worsening DM incidences. There are numerous articles and extensive research had been done on the lifestyle factors focussing on the intervention of diet and exercise. The review identified and compared the effectiveness of lifestyle intervention with respect to diet and exercise in preventing the incidence and prevalence of diabetes or delaying its complications. There were 10 articles that were published in the authorised journals in different years and in different places which were included in the study and were compared for the lifestyle modification on the incidences of diabetes. The modification was basically the prevention of the sedentary lifestyle of the diabetic patients. The results of the studies were compared on the basis of cumulative incidences of diabetes in the intervention group and in the control group. These studies were conducted in different parts of the world in which two studies each were done in Japan in the year 2005 and 2011 and in China in the year 1997 and 2013 respectively. Other studies were done in the USA, Finland, India, Netherland, Australia, and England in different years. All studies advocated the habit of moderate exercise and the healthy diet of low fat and high protein rich diet. This caused the cumulative incidence of diabetes at a low rate in the intervention group than in the control group (normal treatment).

Travel in flight causing jet-lag and lifestyle modification (intervention in diet and exercise), cause the disturbance in the biological rhythms in an individual body separately. This brings the concept of chronobiology and chronopharmacology in the light which is already discussed. There are various defined types of rhythm in our body like ultradian, circadian, infradian, circaseptan, circamensual, and circacannual. It has been observed in various studies done by scientists in the field of chronobiology that there are external factors also that affect the biological rhythms of the person like sleep/wake, warmth/cold, eating/fasting. Thus the time of meal and medication also plays an utmost important role in maintaining the biological rhythms in our body. Any variation may lead to severe health issues. One of the reasons for the occurrence of complications and increase in DM incidences is due to disturbance in chronopharmacology and specifically the disturbance of the circadian rhythm (sleep/wake cycle). Time of light, wavelength, and intensity determines the circadian patterns of the body. Role of melatonin is also discussed that play the major role in circadian rhythm maintenance and hence the severity and worsening of DM condition.

CONCLUSION

Diabetes self management education (DSME) has become an integral part of diabetes care. The combination of lifestyle modification as well as the treatment is extremely essential to combat diabetes[39]. Thus, briefly we can conclude that frequent long-haul travel in different time zones and the sedentary lifestyle can worsen the diabetic incidences. Frequent long-haul travelling must be prevented for diabetic patients as they are prone to metabolic disturbances and poor glycaemic control due to the disturbance in the biological rhythms that regulate the metabolism and conversion of glucose. Pre-advice from general practitioner not taken prior to travelling can cause serious implications of diabetes causing worsening of DM conditions. Usage and storage of insulin are of utmost importance and if not maintained properly then travellers are more susceptible to worsening of diabetic incidence. Implementation of healthy protein rich diet and moderate exercise has the ability to decrease the cumulative incidences of diabetes. As disturbance of the biological clock comes into the light, marking the importance of the study of chronobiology and chronopharmacology and thus there is need of more study and new research to be done to clarify the impact of frequent travelling in different time zones on diabetic patients.

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