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Original Research Article

Evaluation of Glycemic Parameters in Type 2 Diabetic Shift Workers

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Abstract

Diabetes Mellitus (DM) is associated with several short term and long term complications which has led to adverse impact on overall wellbeing of such patients, in the form of severe morbidity and mortality risk. The subjects so included were subjected to a detailed clinical history with special emphasis on duration of illness and treatment history and a thorough clinical examination was done in each case. Quantitative data was expressed by mean and standard deviation and difference of means was observed by t test and qualitative data was expressed as percentages and difference between proportions was observed using appropriate test. 95% confidence level was used to quantify at risk values and factors. The glycemic parameters were significantly deranged in shift workers as compared to non-shift workers, with a difference of almost 4% in hBA1c levels (p value) Similar statistically significant difference was noted in fasting and post prandial blood sugar levels also.

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Introduction

Diabetes mellitus (DM), has emerged as one of the major public health problems worldwide. Patients getting diagnosed with DM have exponentially increased to an extent that it is now taking the shape of an epidemic. DM is associated with several short term and long term complications which has led to adverse impact on overall wellbeing of such patients, in the form of severe morbidity and mortality risk[1-4]. With rising incidence and prevalence of DM, the horizon of understanding this disease has widened over years and so is the scope of various therapeutic modalities. The disease is hallmarked by the gradual and progressive insulin resistance and diminution in the beta cell function. Beta cell function and insulin resistance are the central mechanism in pathogenesis of Type 2 diabetes mellitus [5-7]. With our growing

knowledge in the field of DM, metabolic clock has been linked to its pathogenesis. Thus raising a plot of concern for standardizing the approach in shift workers, in whom metabolic clock has been disrupted. This may further have an impact on not only glucose metabolism, but also on action of various drugs.

Twenty-four hour services are an increasing part of contemporary society. Essential services (i.e., hospital assistance) are provided nonstop, and several industries and business organizations work on a 24 h basis to meet the frequently shifting demands of the contemporary world. Therefore, companies need workers to work incessantly, creating a demand for the shift- and night-work organization. Approximately 20% of the active population in the USA and the EU are occupied in various sorts of shift duties involving night work [8-9].

Shift worker involves irregular or unusual hours of work compared with those of normal day time work schedule, which includes regular evening, night, rotating shifts, and irregular schedules. The biological mechanism associated are basically circadian mismatch, which results in metabolic problems such as increased postprandial glucose, insulin and blood pressure levels, reduced leptin secretion and sleep efficiency and also complete inversion of cortisol profile.[11] The desynchronization of various anabolic and catabolic process is presumed to be altered in shift workers which may have in particular have effect on glucose metabolism.

Night shift work induces mental, behavioural and physiological stress from changes in sleep rhythm and sleep deprivation. Night shift work is closely related to the occurrence of atherosclerosis, diabetes and metabolic syndrome in addition to change in sleep, and is known to be an important cause of cardiovascular diseases [12,13].Sleep deprivation and poor quality sleep disrupts circadian rhythm and autonomic balance. It makes BP control difficult and exacerbates insulin resistance[14,15] With regard to risk of diabetes, prior studies have shown that, impairment of glucose tolerance in shift workers, with increased insulin resistance at night and higher prevalence of type 2 diabetes in relation to rotating shift work, which appears to increase with years spent doing shift work [16,17]. Hence with increasing prevalence of type 2 diabetes, understanding the aspects of shift work schedule is required for designing targeted primary and secondary preventive strategy. Thus, the present study was conducted to greater significance especially in hilly areas of Uttarakhand where in addition to day and night shift works in various occupations, day and night time variations and change in exposure to sunlight also occurs which may have an impact on the diseases.

Methodology

The subjects so included were subjected to a detailed clinical history with special emphasis on duration of illness and treatment history and a thorough clinical examination was done in each case. The diagnosis of Diabetes was based on ADA guidelines (2014). These subjects were categorized in 2 groups: An informed written consent from the patient and/or legal guardian was taken from all the patients included in the study. These subjects were categorized into group A (30 patients with type 2 diabetes not having any shift duty or similar life style) and group B (30 patients with type 2 diabetes having shift duties or life style similar to shift duties)

Night Shift Worker: Defined as subject whose waking period /active duty hours are at least 12:00 am to 6:00 am.

Non–Shift Workers: Defined as those who have normal sleep pattern elicited through history between 12:00 am to 6:00 am.

Study Duration: Study was carried out between December 2018 to November 2020

Study Site: Shri Mahant Indiresh Hospital, Patel Nagar, Dehradun.

Study Design: Cross sectional study

Inclusion Criteria:

1. Age > 18 yrs.
2. Type 2 Diabetes
3. Shift worker

Exclusion Criteria:

1. Type 1 Diabetes
2. Secondary diabetes
3. Gestational diabetes
4. Chronic renal failure
5. Chronic liver disease
6. Obstructive sleep apnoea / central sleep apnoea syndromes
7. Any other metabolic disorder likely to alter sleep pattern

Study Planning:

A thorough history was taken with special emphasis on knowing occupation and sleep pattern. They were clinically examined, especially for any existing diabetes complications. They were investigated, especially for any existing diabetes complications. They were investigated as per protocol of diabetes clinic: All patient were investigated for FBS, PPBS, S. INSULIN LEVEL, HBA1C Additional investigation were done as per requirements.

Study Technique:

FOR Fasting Blood Sugar (FBS) - 5 ml of fasting blood sample was collected and centrifuged for serum/plasma separation. Sample was analyzed for the measurement of plasma glucose by glucose oxidase - peroxidase method,

For HBA1C -Whole blood was taken in EDTA vial for HbA1c by ion-exchange resin method.

For Fasting Insulin - was calculated with Vitros 5600 full automated by enhanced chemiluminescence.

HOMA IR= FASTING GLUCOSE X FASTING INSULIN

*HOMA-Homeostatic model assessment
1) IR-Insulin Resistance
2) B-Beta cell function

Ethical Clearance

Ethical clearance was obtained before conducting the study from the Institutional Ethical Committee of SGRRIM & HS, Dehradun.

Statistical Analysis

The collected data was entered in MS excel and was then analyzed using SPSS latest version. Quantitative data was expressed by mean and standard deviation and difference of means was observed by t test and qualitative data was expressed as percentages and difference between proportions was observed using appropriate test. 95% confidence level was used to quantify at risk values and factors.

Results

Table 1: Comparison of glycemic parameters in type II DM shift and non-shift workers

Baseline characteristics (N=30)	Shift		Non-shift		P value
	Mean	SD	Mean	SD	
age	53.10	8.56	59.53	10.36	<0.001*
Duration of diabetes	14.03	6.41	17.01	6.58	<0.001*
Shift years	19.20	7.59	-	-	
FBS	202.50	46.84	121.93	22.35	<0.001*
PPBS	264.10	55.88	156.70	34.07	<0.001*
HbA1c	11.18	2.58	7.32	.94	<0.001*
Fasting insulin	10.10	1.56	7.33	1.51	<0.001*
HOMA IR	4.03	1.64	2.22	0.58	<0.001*

Table 1 shows that mean FBS was found to be higher in shift worker as compared to non-shift worker. Mean PPBS was found to be higher for shift worker as compared to non-shift workers. Mean HbA1C was found to be higher for shift worker as compared to non-shift worker. Fasting insulin was found to be higher in shift worker as compared to non-shift worker. HOMA IR was found to be higher in shift worker as compared to non-shift workers. All the five parameters was found to be statistically significant.

Table 2: Comparison of FBS in type-II DM among shift and non-shift workers according to age

Age in Years	Shift Workers		Non-Shift Workers		P value
	N	Mean ± SD	Numbers	Mean ± SD	
<40	3	183 ± 21	1	120	
41-50	8	226 ± 62	4	127 ± 26.94	<0.05
51-60	14	204 ± 41	15	122± 23.42	<0.01
>60	5	174 ±34	10	119 ± 22.2	<0.01

Table 2 shows that in all age group of patients mean FBS was higher in shift worker as compared to non-shift workers and statistically significant.

Table 3: Comparison of PPBS in type-II DM among shift and non-shift workers according to age

Age in Years	Shift Workers		Non-Shift Workers		P value
	N	Mean ± SD	Numbers	Mean ± SD	
<40	3	257 ± 12	1	150	
41-50	8	276 ± 59	4	168± 46	<0.01
51-60	14	268 ± 66	15	153± 30	<0.01
>60	5	239±32	10	158 ± 39	<0.01

Table 3 shows that in all age group of patients mean PPBS was higher in shift worker as compared to non-shift workers and statistically significant.

Table 4: Comparison of HbA1c in type-II DM among shift and non-shift workers according to age

Age in Years	Shift Workers		Non-Shift Workers		P value
	N	Mean ± SD	Numbers	Mean ± SD	
<40	3	10 ± 2	1	7	
41-50	8	12± 1.7	4	8± 0.9	<0.01
51-60	14	11± 3.1	15	7± 0.7	<0.01
>60	5	10±2.2	10	7± 1.3	<0.01

Table 4 shows that in all age group of patients mean HbA1c was higher in shift worker as compared to non-shift workers and statistically significant.

Table 5: Comparison of Fasting insulin in type-II DM among shift and non-shift workers according to age

Age in Years	Shift Workers		Non-Shift Workers		P value
	N	Mean ± SD	Numbers	Mean ± SD	
<40	3	12 ± 2.64	1	9.0	
41-50	8	10 ±1.93	4	8.0± 2.16	<0.01
51-60	14	9.79 ± 1.19	15	6.60± 1.24	<0.01
>60	5	10.0	10	7.98 ±1.25	<0.01

Table 5 shows that in all age group of patients mean Fasting insulin was higher in shift worker as compared to non-shift workers and statistically significant.

Table 6: Comparison of HOMA IR in Type II DM shift and non-shift workers.

Age in Years	n	HOMA IR (Shift workers) Mean ± SD	n	Non-shift workers Mean ±SD	P Value
<40	3	4.73 ± 2.4	1	1.9	
41-50	8	4.46 ± 2.4	4	2.31 ± 0.7	0.04
51-60	14	3.48 ± 1.1	15	2.16 ±0.6	<0.001*
>60	5	4.28 ±0.8	10	2.29 ±0.6	<0.01*

Table 6 shows that in all age group of patients mean HOMA IR was higher in shift worker as compared to non-shift workers and statistically significant.

Discussion

The Ministry of employment and Labor defines night work as performing 8 hours of work between 10 pm and 6 am the next day that includes continuous work for at least 5 hours between midnight and 5 am for at least 4 times a month and for a total of 6 months, or performing between 10 pm and 6 am the next day for more than 60 hours per month on average for 6 months[10].

The definition used for shift worker in our study would enable subjects to have a reasonable diurnal circadian shift and re adjustment of the neurohormonal mechanisms.

This study was planned with background that circadian rhythm modulates various hormonal cascades which may have bearing on various metabolic pathways, expression of enzymes, expression and secretion of various hormones. These alteration are likely to affect the glycemic status in diabetics.

In the study population, shift workers were defined as those doing night shift at least 6 hours between (12 AM and 6 AM) for at least 15 days in a month. This pattern is sufficient to disrupt the normal diurnal pattern. The glycemic parameters were significantly deranged in shift workers as compared to non-shift workers, with a difference of almost 4% in hBA1c levels (p value) Similar statistically significant difference was noted in fasting and post prandial blood sugar levels also.

These findings are in agreement with Morshead et al. demonstrated that patient with type 2 diabetes who performed overnight work had significantly worse glycemic control as assessed by HbA1c than those not performing day work, after adjusting for multiple factors including sleep-duration, morning-evening preferences and diet. Night shift workers was associated with 5.9% increase in HbA1c of its original value.[18]

A measurement of fasting, postprandial blood glucose, glycated hemoglobin (HbA1c) and albumin creatinine ratio (ACR) was applied. The study revealed that shift work group, in comparison for daytime work group, has higher body mass index (BMI) 32.2(3.2) vs. 28.2(2.4) (P<0.05), poor-sleep-quality 54 (71.1%) vs. 6(7.9%) (P<0.05) and higher HbA1c9.8(1.2) vs. 8.1(1.3) (P < 0.05). In spite of the higher percentage of diabetic retinopathy, nephropathy, the difference was only significant for diabetic neuropathy. Shift work adversely affect diabetic control and deteriorate measured HbA1c; and increase the incidence of microvascular complication. [19]

Ghazawy et al. (2014) observed that rotating night shift especially night shifts have a negative impact on health. It was found to be associated with developing type 2 diabetes mellitus and it hindered diabetes control among night shift diabetic workers [20].

Anu Sharma et al(2017) also had similar observation however they had focused more on post prandial glucose disruption and C-peptide levels after meals. Sad et al (2012) observed a diurnal pattern of Beta cell function in non-diabetic Patients. They also observe that despite higher post prandial blood sugar during night shift, glucagon suppression was delayed compared to night shift but actual value did not differ[21].

Varma et al. (2002) observed that the melatonin value begin to peak around 2:00 am and the levels are suppressed by sunlight through the supra-chaismatic pathway. He also observed that the duration of day and night and prolonged dark phase is associated with increase in melatonin value and also melatonin resistance. Melatonin may also be one of major mediator between light at night and abnormal glucose metabolism. Besides, presence of white light at night, availability of food at different times and nature of food may also be important factors in misalignment of circadian rhythm[22].

It is observed that by the time the disease is diagnosed, there is deterioration of more than 50% of beta cell mass. Hence, beta cell dysfunction and insulin resistance are the central mechanism in the pathogenesis of T2DM. As a surrogate marker for measuring beta-cell function and insulin sensitivity, the homoeostasis model assessment (HOMA) indexes, which are based on fasting glucose and insulin levels, have been widely used.

In this study it is being observed that mean HOMA IR index is significantly higher in shift worker as compared to non-shift workers with a significant p value.(Table) Our study is in accordance with Ledda et al (2019) who assessed that Indicators of glucose metabolism were significantly higher in HCSW $p < 0.001$, and logistic regression analysis confirmed a significant positive association between increased values of HOMA-IR Index and shift workers ($p < 0.05$)[23]

Marta Garaulet et al [24] opined that low urinary levels of primary metabolite of Melatonin, 6 sulfatoxy melatonin have been prospectively associated with increase in insulin resistance and risk of type 2 DM. Also, in patient with type 2 DM and insomnia, a significant decrease in HbA1c levels was found after 5 months trial of repeated night time melatonin. However they did not consider the serum plasma value and depended upon urinary levels of metabolites, which at best represented the pooled values of the hormones. Since the serum values of melatonin (and hence its metabolites) surge around 2:00 AM TO 3:00 AM, and the values get suppressed within 1 hour of exposure to sunlight. It is also imperative to consider the phenomena of melatonin resistance in such group.(Amit et al 2002)

This observation implies that the expression of melatonin and other neurohormonal substances is intact in different age groups. This observation is significant due to the fact that with aging the expression of night time melatonin levels are suppressed in elderly and further its suppression with exposure to light is also reduced. A large scale study may needed to underline these observations.

These circadian difference may be understood by the universal fact that rotation of earth around its axis exposes different organisms on either side of equator to different degrees and extent of rotation. This would in turn lead to variation of exposure to light and dark phases, further these light and dark changes lead to variation of exposure to light and dark changes lead to subtle changes in metabolism, metabolic pathway, action of various enzymes and co enzymes and neurohumoral circuits. These changes align themselves with the environmental cues or Zeitgebers (time givers). This light and dark phases lead to changes in sleep and

wake cycle and also on fasting and feeding cycle. These are two most important behaviour which determines the energy demand and nutritional supply.

These two arms (energy demand and nutritional supply) oscillates depending upon the sleep and non-sleep phases. These factors in turn, determines the body temperature, glucose utilization, lipid metabolism and feeding related hormones and this synchrony or alignment in turn is translated to survival advantage [14]. This also implies a concept of external and internal clock and also their alignment. A asynchrony between them may lead to wide range of disturbances both in term of expression of disease and probably pharmaceutical management.

These Intercellular mechanism is conserved by auto regulatory transcription translation feedback loop generated by CLOCK proteins which influence transcription factors. CLOCK and BMAL encodes basic Helix - loop helix, Per- ARNT single muscle protein that initiate transcription by binding to promotor region of target gene on one hand and other hand PER and CRY gene which are responsible to translocate Nucleus upon translation and where they function as negative regulator of their own transcription.

The peripheral clock are thus conceptualize in organ like pancreas, liver and lungs and central clock governed by SCN. While the primary environmental cue modulates SCN clock in light, peripheral clock are believed to be responsive to variety of signals including autonomic nervous system control by SCN, neurohumoral signals as well as indirect signals such as alteration in body temperature and timing of food intake.

Changes further, glucose availability and subsequent changes alter CLOCK gene expression in pancreatic islet cells, oscillation of intercellular redox state due to metabolic changes affect CLOCK and BMAL , ANP dependent kinase mediated phosphorylation and degradation of CLOCK protein yet another mechanism responsible for feeding induced entrainment of islet cell clock, further ingestion of other food generated metabolite like amino acids, lipids, ketones are capable of intracellular metabolic environment and also contribute to resetting islet cells oscillation.

In our study many of diabetics were on incretins, these incretins have recently been shown to demonstrate their secretion is under CLOCK control, high expression of incretin receptors in islets and also fact that incretin activate CAMP- pCREB intracellular signalling cascade known to be important for CLOCK entrailment[25]. Autocrine effects of insulin release may also contribute to islet clock entrainment Since insulin had recently shown to entrain circadian oscillators in liver [26].

There has been growing evidence to suggest the role of desynchrony in worsening of glycemic control for example Dawn phenomena where increase in blood sugar in diabetics or increase in insulin secretion in healthy subjects occur in early waking period. Since this phenomena occurs 7-9 hours after fasting so unlikely to be food driven.

At molecular levels, this association was clearly demonstrated in animal model using CLOCK mutant mice, BMAL knock out mice, Per2 mutant mice and Cry Deficit mice studies. It has been inferred that CLOCK gene are involved in hepatic. Glucose storage transport and export by regulating circadian expression of GLUT2, glucokinase and pyruvate kinase in liver. CLOCK gene preserves normal beta cell function by preventing ROS accumlation via activation of several antioxidants genes. They prepare muscle cells for transition from lipid to glucose metabolism by increasing insulin stimulated glucose uptake. CLOCK gene regulates the plasma concentration of PUFA which affects expression of neurotransmitter responsible

for appetite regulation in hypothalamus feeding centre.

Conclusion

Type 2 diabetes mellitus is a modern worldwide epidemic. Its complications are a significant causes of morbidity and mortality and the consequences of its explosive growth are an intolerable burden both to the individual and to health care system. Modern society is moving towards a pattern of working twenty four hours a day and shift work that includes a night time rotation has become an unavoidable attitude of todays 24 hr society. Shift work contributes to development of diabetes and other metabolic disorder through a number of pathways including circadian rhythm disruption, life style changes, job strain and social stress.

Glycemic parameters were markedly deranged in shift worker as compared to non-shift workers. The glycemic parameters did not differ in different age group.

The study has a great significance in the ongoing urbanization where there is increasing need for shift work owing to increase work demand and increasing productivity. It is important to understand the underlying neurohormonal mechanisms which may have a long term bearing. Secondly those living in hill areas especially at higher altitude have a significant day and night (light and dark phase variation) and the neurohormonal mechanism may act similarly, especially in type 2 diabetics. These observations would prompt to suggest alternative life styles, finer changes in work adjustment and therapeutic modalities for management of disease.

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