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Research Article

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Circadian Disruption of Melatonin among Night Shift Workers and Its Effect on Glycemic Variability

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Abstract: Melatonin is a pineal gland secreted hormone controlling sleep wakefullness. Light is a stimulus and hence this hormone exhibits circadian rhythm. Melatonin has pleiotropic effects on carbohydrate and lipid metabolisms. Glycemic variability is defined as variations in interstitial glucose levels measured every 15 seconds using a sensor-based technique. It is the result of constant carbohydrate metabolism and insulin action. Melatonin also has rhythms that are more akin to a nocturnal hormone. It affects glycemic variability. Variability is associated with a very high cardiac risk factor. Melatonin rhythm may be disrupted in night shift workers as a result of light exposure during the night, with implications for insulin secretion and glycemic variability. Correlation provides greater insight into the rhythmic hormonal activity and altered glucose homeostasis that predispose to diabetes, and thus this study was done to establish the correlation. This study was done to evaluate the effect of melatonin levels on altering glycemic control among night shift workers. This case control study included 40night shift workers both male and female (cases) aged 25-35years and 40 healthy controls of same age group. Blood samples for melatonin estimation were collected at 9PM and 6AM (after night shift work) by venepuncture and serum separated. Serum melatonin levels were estimated by ELISA method. Fasting and post prandial blood glucose were estimated by GOD-POD method and glycemic variability analyzed by Abbott biosensors. Data was analyzed using SPSS package. Night shift workers were found to have decreased melatonin levels and altered blood glucose levels compared to the control group. Melatonin has a negative influence on glycemic variability. This fact was evidenced in our study. Hence this study will help us to understand and intervene.

Keywords: Melatonin, ELISA, Abbott Biosensors

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1. INTRODUCTION

Melatonin (N-acetyl-5-methoxytryptamine), an endocrine agent derived from tryptophan, is primarily synthesized by the pineal gland and, to a lesser extent, by a variety of other tissues[1]. Melatonin, also known as the "darkness hormone," is primarily secreted by the pineal gland, with levels being highest at night and lowest during the day[2]. It has an antioxidant effect as well as regulating the circadian cycle. Diabetes mellitus is a metabolic disorder caused by insulin deficiency or resistance. The majority of cases are diagnosed using plasma glucose samples and Hba1c levels. Currently, sensor-based assessment of glycemic variability provides ambulant monitoring of glucose levels in the interstitial fluid 24 hours a day, seven days a week. This will greatly assist diabetic management in terms of overall glycemic control. Melatonin secretion influences the glycemic variability and pulsatile nature of insulin secretion, which controls blood sugar levels[3]. This hormone has a circadian rhythm and is secreted at its peak at 3 a.m., so it was sampled at that time without being exposed to light. Sleep-wake cycle disruption reduces melatonin secretion and may be linked to sleep disorders and diabetes. Melatonin inhibits the cAMP and cGMP pathways, which are mediated by Gi protein-coupled MT1 receptors[4], and thus reduces insulin secretion. Glucose is required as a stimuli for proper insulin secretion by pancreatic beta cells. If the melatonin rhythm is disrupted, the normal pulsatile insulin response curve may be lost, resulting in glycemic variability that fluctuates between high and low values[5]. This is extremely harmful. Ideally, because melatonin is expected to be secreted less in night shift workers who have turned their nights into days by using artificial lights. The study aimed to determine whether night shift workers are at a higher risk of developing diabetes or complications from diabetes due to extreme glycemic variability by correlating their serum melatonin with glycemic variability. The circadian rhythm refers to the changing rate of activity over each 24-hour period. A person who works at night or begins their working day before 6 a.m. is disrupting their circadian rhythm. This may put them at risk of developing health issues. Many trials have shown, however, that microvascular and macrovascular complications are primarily or partially dependent on dysglycemia, which has two components: chronic sustained hyperglycemia and acute glycemic fluctuations from peaks to nadirs[6,7]. Both components contribute to diabetes complications via two main mechanisms: excessive protein glycation and oxidative stress activation. Light exposure at night shift decrease the melatonin production due to acute suppression of pineal melatonin secretion and leads to increased insulin secretion at night and insulin resistance. With this background this study was aimed to understand the correlation between serum melatonin and glycemic variability (is a better reflector of oscillations in glucose levels 24/7) among night shift workers.

2. MATERIALS AND METHODS

This case control study was conducted in the Department of Biochemistry, Sree Balaji Medical College and Hospital, Chrompet, Chennai during the period of January 2019 – March 2019. The ground work for the study was started after getting clearance from the research committee and the Institutional human ethical committee (reference number for approval: 002/SBMC/IHEC/2017-931) of Sree Balaji Medical College and Hospital, Chrompet, Chennai. This study included 40 non diabetic night shift workers both male and female (cases) aged 25-35years and 40 age, gender matched participants (controls) who had regular sleep pattern at night. The night shift workers were in similar work for 2 years. Age, gender, height, weight, BMI, general history, family history, medications and blood pressure were recorded. Routine clinical examination was done. The study was explained to the participants and informed consent obtained from them before taking the blood sample. Blood samples for melatonin estimation were collected at 9PM and 6AM (after night shift work) from participants of both the groups by venepuncture and serum separated. Samples were analyzed for 6-Sulfatoxy Melatonin by ELISA method[8]. Fasting and post prandial blood glucose were estimated by GOD-POD method. HbA1C was estimated by Immunoturbidimetry method[9]. In both the groups, 24 hours glycemic variability was estimated with help of Abbott Biosensors[10].

2.1 Inclusion Criteria

- Subjects of age between 25-35 years, both genders equal numbers working continuous 7 days of rotating night shift with light exposure each month.
- The subjects were randomly selected from staff nurses and technologists
- Subjects were investigated by master health check up scheme and recruited after found to be healthy

2.2 Exclusion Criteria

- Age group less than 25 years and greater than 35 years
- Subjects with any acute/chronic illness, Diabetes mellitus, Endocrinal disorders, Hypertension, coronary artery disease and chronic renal disease.

2.3 Sample Collection

The blood samples were collected from subjects by venepuncture under aseptic precautions in specific vacutainers. Fluoride tube for blood glucose, plain tube for melatonin, EDTA sample for HbA1C were used. Both fasting (12 hours overnight fasting) and post prandial samples were collected.

3. STATISTICAL ANALYSIS

The characteristics of study participants are summarized using mean and standard deviation. The outcome variables namely, fasting plasma glucose, postprandial plasma glucose, glycated hemoglobin (HbA1c), serum melatonin were compared between the cases and controls using independent t-test. A two sided p-value less than 0.05 was considered to be statistically significant. The analysis was conducted using SPSS version 20.

4. RESULTS

The study participants were 40 non diabetic night shift workers both male and female (cases) and 40 age, gender matched participants(controls) who had regular sleep pattern at night All study participants were in the age range of 25-35years. The normal serum melatonin levels, at night 80–100 pg/mL and during the day 10–20 pg/mL[11].

Table 1: Characteristics of study participants		
	Cases (Mean ± SD)	Control (Mean ± SD)
AGE in years	23.75 ± 1.05	23.87± 1.88

SD- standard deviation. The mean age of cases was 23.75 ± 1.05 years and the controls 23.87± 1.88.

Table 2: Comparison of melatonin levels between cases and controls			
	Cases (Mean ± SD)	Control (Mean ± SD)	p-Value*
Night (11pm) Melatonin (pg/ml)	19.68 ± 4.12	48.68 ± 6.85	P value < 0.0001
Morning (6am) Melatonin (pg/ml)	22.20 ± 1.33	26.92 ± 2.46	P value = 0.0007

The mean of serum melatonin levels of cases and controls at night were 19.68 ± 4.12 and 48.68 ± 6.85.as suggested in table no 2 The mean of serum melatonin levels of cases and controls at morning were 22.20 ± 1.33 and 26.92 ± 2.46. The mean of serum melatonin levels of cases were found to be reduced in night and morning when compared with the controls and was significantly different between cases and controls with statistically significant p values of <0.05.The mean glycemic variability as suggested by table no 3 suggests that mean glycemic variability among cases (night shift workers)102.56 were higher than controls 91.0

Table 3: Comparison of HbA1C levels and glycemic variability between cases and controls			
	Cases (Mean ± SD)	Control (Mean ± SD)	p-Value*
HbA1C	5.86 ± 0.29	5.21 ± 0.21	P value = 0.0010
Mean glycemic variability	102.56 ± 3.26	91.0 ± 5.83	P value = 0.0002

HbA1c levels in cases were high in cases of about prediabetic range (5.86 ± 0.29). High glycemic variability was observed in cases at night (102.56 ± 3.26). P- value was statistically significant <0.05.

5. DISCUSSION

Melatonin, also known as the third eye, is produced by the pineal gland from the amino acid tryptophan via a series of enzymatic reactions and transmethylation reactions from serotonin[12,13]. Melatonin is a lipophilic substance that is broken down into several compounds in the liver and the central nervous system. Melatonin regulates circadian rhythm and phase shift by acting on almost all cells in the body via feedback on suprachiasmatic nuclei by MT1 and MT2 receptors[14]. In healthy men, the half-life of blood melatonin is less than 30 minutes[15], and the metabolic clearance is 630 mL/min. Melatonin receptors are also found in peripheral tissues such as the liver, muscle, and pancreas, where they help to regulate glucose homeostasis and body weight. [16]. This study shows the melatonin levels at night among the night shift workers had reduced than the controls. Tao Wei et al, in their systemic review and meta analysis on association between night shift workers and melatonin has mentioned that melatonin levels in night-shift workers was significantly lower than in day workers[17]. Melatonin has an effect on diabetes and metabolic dysregulation by regulating insulin secretion and scavenging reactive oxygen species. Pancreatic -cells are highly vulnerable to oxidative stress and have a low antioxidative potential. Diabetes is linked to a phase shift in the cardiac circadian clock. Human MT2 receptor polymorphisms have been linked to an increased risk of developing type 2 diabetes [18]. Night work has been linked to decreased sleep duration. Light exposure at night and rotating night shifts reduce melatonin production due to acute suppression of pineal melatonin secretion, raising the risk of endocrine disorders. Circadian rhythms govern sleep/wake cycles, sexual behaviour and reproduction, thermoregulation, glucose metabolism, lipid metabolism, energy intake/expenditure, and food and water intake[19]. Changes in feeding or sleeping patterns, as well as exposure to light at unusual times during the night, known as "light-at-night pollution," disrupt the circadian clock and cause metabolic disruption. This is seen in patients with hypertension, diabetes, obesity, and shift workers, all of whom have an increased risk of cardiovascular disease. Shift workers and time zone travelers experience abrupt changes in the light-dark cycle, and the list of associated risks is lengthy (increased rate of accidents, decreased alertness and performance, gut problems, increased risk for metabolic diseases, etc)[20]. Melatonin deficiency affects the functional association between melatonin and insulin, as evidenced by the fact that pinealectomy-induced insulin resistance and glucose intolerance are linked at the molecular level as a deficiency in the insulin-signaling pathway and a decrease in GLUT4 gene expression and protein content. Melatonin, acting through MT1 membrane receptors, causes rapid tyrosine phosphorylation and activation of the insulin receptor's tyrosine kinase beta-subunit, overcoming several intracellular transduction steps of the insulin-signaling pathway [21]. Melatonin influences overall metabolism by influencing adipose tissue. Melatonin activates MT2 receptors in human adipocytes, modulating glucose uptake. This explains melatonin's synergistic effect on several other insulin actions, such as glucose uptake: insulin-induced leptin synthesis and release in isolated adipocytes via MT1-mediated melatonin action, and melatonin regulates other aspects of adipocyte biology that influence energy metabolism, lipidemia, and body weight, such as lipolysis, lipogenesis, adipocyte differentiation, and fatty acid uptake. Melatonin stimulates glucose uptake in muscle cells via MT2 signalling by phosphorylating insulin receptor substrate-1. Hepatocytes express MT2 receptors, which promote glycogenesis. Another important site of melatonin action in energy metabolism regulation is the pancreatic islets, where it influences insulin and glucagon synthesis and release[22]. The observation that insulin secretion is inversely proportional to plasma melatonin concentration could explain the link between melatonin and type 2 diabetes. These two hormones, melatonin and insulin, have a circadian rhythm, but their synthesis dynamics are negatively correlated.

Gluconeogenesis and glyconenolysis have a circadian rhythm in type 2 diabetics. The suppression of melatonin secretion by nocturnal light exposure may be a risk factor for the development of type 2 diabetes[23]. Hyperglycemic clamps and experiments on isolated pancreatic islets have shown that glucose induces insulin secretion in a biphasic pattern: an initial component (first phase) that develops quickly but only lasts a few minutes, followed by a sustained component (second phase) [24]. Type 2 diabetes mellitus (T2DM) is characterised by loss of first-phase secretion and reduced second-phase secretion; it is well known that a decrease in the first phase of GSIS is found in the early stages of T2DM as well as impaired glucose tolerance[25]. Thus, insulin secretion oscillations are most likely caused by intrinsic cell mechanisms and influenced by exogenous signals such as hormonal and neuronal inputs. Based on previous research and our findings, a comprehensive understanding of the mechanism of oscillatory insulin secretion, the effects of melatonin on glucose and lipid metabolisms, and a clear relationship between circadian hormone and glycemic variability could be established. As seen in table 3 this research supports the findings and hypothesis that there is a clear positive relationship between serum melatonin levels and glycemic variability. Glycemic variability provides a more complete picture of oscillatory insulin dynamics and related glucose changes. As a result, biosensor-based interstitial glucose monitoring was chosen as a method for determining changes in glucose levels that oscillate with the circadian rhythm. Subjects were recruited whose oscillatory rhythms of melatonin and glucose levels were disrupted due to changes in work schedules. According to the findings of this study, night shift workers have lower levels of melatonin at night and in the morning. In their study, Peplonska et al found that working a night shift of six to eight hours or more alters the synthesis of melatonin[26]. As a result, night shift workers have altered melatonin circadian rhythms. Diabetes is more likely to occur when circadian patterns are disrupted. In the current study, night shift workers had higher HbA1C levels in the pre-diabetic range of ADA criteria and higher glycemic variability at night than controls. In their study, Prokopenko I et al discovered that type 2 diabetic patients had low levels of circulating melatonin[27]. This is also clearly demonstrated in our study by the fact that night shift workers had altered circadian rhythms, as evidenced by altered insulin secretory patterns and gross glycemic variability when compared to age-matched controls. Moreover, numerous studies have found a link between sleep disorders and an increased risk of impaired glucose tolerance and type 2 diabetes.[28] Self care knowledge on diabetes among diabetic patients is very much important for effective blood glucose control

6. CONCLUSION

The decline in melatonin synthesis associated with shift-work or illuminated environments during the night, induces insulin resistance, glucose intolerance, sleep disturbances and metabolic circadian disorganization, and metabolic imbalances, aggravating the general health state. Melatonin supplementation may have beneficial effects on glucose homeostasis. It would advance the current therapeutic strategy to overcome the diabetes effects which is currently prescribed for sleep and circadian rhythm. This study has established an association between serum melatonin and glycemic variability .Glycemic variability has an adverse influence on cardiovascular system even more than sustained high glucose levels in the blood .Since we understand that serum melatonin plays a great role in glycemic variability. Endocrinologists when faced with challenges of insulin resistance should consider the role of melatonin, include measurement of serum melatonin as a protocol and plan lifestyle modifications and therapeutic interventions accordingly

7. AUTHORS CONTRIBUTION STATEMENT

This study was done by Dr. Mary Chandrika Anton under the guidance of Dr. B. Shanthi. Sample collection, analysis was done by Dr. Mary Chandrika Anton. Review of literature was done by Dr. B. Shanthi.

8. ACKNOWLEDGEMENT

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9. ETHICAL STANDARDS

The study involved human participants following the ethical standards of the tertiary health care institution where the study was conducted.

10. LIMITATIONS OF THE STUDY

The study population shall be enlarged as it was relatively less.

11. FUNDING ACKNOWLEDGEMENT

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12. CONFLICT OF INTEREST

Conflict of interest declared none.

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