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CORRELATION OF SERUM MELATONIN AND SERUM HIGH SENSITIVITY C- REACTIVE PROTEIN (hs-CRP) IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

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Abstract

Background: Type 2 Diabetes Mellitus (T2DM) presents as a complex metabolic disorder characterized by insulin resistance alongside chronic low-grade inflammation. Melatonin, primarily synthesized by the pineal gland, serves as a key regulator in various physiological functions, such as the sleep-wake cycle and immune response. Recent research indicates a promising connection between melatonin and both glucose metabolism and inflammation. In T2DM, elevated levels of high sensitivity C-Reactive Protein (hs-CRP), a sensitive marker of systemic inflammation, are commonly observed. Investigating the relationship between Serum Melatonin and hs-CRP levels in individuals with T2DM may provide crucial insights into melatonin's potential role in modulating inflammation and metabolic dysregulation in T2DM. **Aim and Objectives:** Correlation between Serum Melatonin and Serum high sensitivity C- Reactive Protein (hs-CRP) in patients with T2DM. **Material and Methods:** A cross sectional study, 104 Type 2 Diabetic subjects were included. Fasting Blood Glucose was measured by semiauto analyser (STAR 21 plus) and Serum Melatonin and Serum hs-CRP level were measured by ELISA. **Results:** FBG showed significant positive correlation with Serum hs-CRP level (r= 0.347, p-value <0.001) & significant negative correlation with Serum Melatonin level (r= -0.370, p-value <0.001). **Conclusion:** This study concluded that Serum Melatonin levels decreased and Serum hs-CRP levels increased significantly in T2DM, indicating a potential association between decreased Serum Melatonin and increased T2DM risk, alongside a possible link between Serum hs-CRP and Diabetes.

Keywords: Diabetes Mellitus, Fasting Blood Glucose, Serum Melatonin and Serum hs-CRP.

INTRODUCTION

Diabetes Mellitus (DM) represents a worldwide health concern. An estimated 537 million persons between the ages of 20 and 79 are affected by it globally (10.5% of all adults in this age range) [1]. According to the Ministry of Health and Family Welfare's (MoHFW) National Family Health Survey-V (NFHS-5) from 2019 to 2021, 10.0% of women and 11.6% of men in Uttar Pradesh have T2DM [2]. DM is a prolonged condition in which the blood glucose level gets elevated than its normal range (i.e.70-110 mg/dl) and termed as Hyperglycemia [3]. The pineal gland secretes the neuroendocrine hormone melatonin. It primarily maintains normal "Sleep Awakening Cycle" and is responsible for maintaining circadian biological rhythm of the human body [4]. It is a

tryptophan derivative and an endogenous antioxidant [5]. Melatonin controls and influences the functioning of several organs, and it is useful in managing immune system function and reducing stress [3]. Insulin Resistance (IR)-induced T2DM has been demonstrated to progress due in part to disruption of melatonin signaling [6]. It was shown that individuals with type 2 diabetes had noticeably reduced serum melatonin levels. Therefore, as melatonin has the effect of inducing a shift in insulin secretion, it may be considered to have an influence on the development of diabetes. An essential feature of T2DM is dysregulation of body insulin secretion [3]. Melatonin has two distinct receptors, MT1 and MT2, which are encoded by MTRN1A and MTRN1B; respectively Melatonin induces the dissociation of the α and β subunits of MT1 and MT2. Subsequently, this division initiates the stimulation of subsequent signalling pathways, such as Phospholipase A2 (PLA2), Phospholipase C (PLC), and Adenylyl Cyclase (AC). Studies have demonstrated that disruptions in melatonin signalling have a role in the pathogenesis of IR-induced T2DM. Aetiology of T2DM and obesity is intricately linked to the disturbance of sleep patterns and the circadian rhythm. These findings suggest that individuals with atypical lifestyles, such as those who work night shifts or have unorthodox eating patterns, are at an elevated risk of experiencing metabolic problems. A study done by McMullan et.al (2013) suggests that inadequate synthesis of melatonin or decreased melatonin signalling may impede insulin sensitivity and contribute to the onset of T2DM [7]. Melatonin modulates insulin secretion and offers protection against reactive oxygen species, which can affect diabetes mellitus and related metabolic disorders. The limited capacity of pancreatic ß-cells to protect themselves from oxidative stress is the reason behind this. Patients with diabetes mellitus exhibited a notable reduction in melatonin levels in their blood [8,9].

The liver synthesizes C - reactive protein, is a non-immunoglobulin and pentameric protein recognized as the "golden marker for inflammation." consisting of five identical subunits [10]. The liver produces hs-CRP, a non-specific inflammatory marker, in response to pro-inflammatory cytokines that come from a variety of sources, including adipocytes [11]. Diabetes is condition marked by persistent low-grade inflammation. Many studies have demonstrated that the diabetic population has considerably higher levels of inflammatory markers in their blood, such as hs-CRP, plasminogen activator inhibitor-1 (PAI-1) fibrinogen, and IL-6 [12]. A recent meta-analysis comprising of twelve prospective studies revealed a correlation between elevated baseline CRP levels and future T2DM, Insulin Resistance, and elevated HbA1c values [13]. Gohel and Chacko et.al (2013) found significant elevated in concentration of hs-CRP in T2DM compared to healthy person [14]. Amanullah et.al (2010) in his study showed significant increase of hs-CRP in patients with T2DM [10]. In addition, there can be a significant association between Type 2 diabetes problems and CRP through the acute phase response [15].

MATERIAL AND METHODS

The study was carried out in the Department of Biochemistry & Central Research Laboratory, School of Medical Sciences and Research (SMS&R), Sharda University, Greater Noida, INDIA. After obtaining ethical clearance.

Inclusion Criteria: - Patients attending the medical OPD of Sharda Hospital Greater Noida, diagnosed as Type 2 Diabetes Mellitus as per the WHO criteria (>126 mg/dl fasting blood glucose) [16], willing to participate in the study and consented for it.

Exclusion Criteria: Under or above the age criteria, Pregnancy, T1DM and Patients with co-morbidity without T2DM.

BIOCHEMICAL ANALYSIS

The participant's blood was taken after an overnight fast of at least eight hours. Samples of serum and plasma were divided and kept at -20 °C for examination. On the same day, samples were analyzed for fasting blood glucose (FBG) measurements. Using a semi-auto analyzer (STAR 21 plus), the GOD-POD approach was used to estimate the blood glucose while fasting. The ELISA method was used to estimate serum levels of hs-CRP and melatonin.

STATISTICAL ANALYSIS

The statistical analysis employed descriptive and inferential statistics, and the mean, standard deviation. Significant results are those with a p-value derived at a 95% level of reliability of less than 0.05. An extremely significant p-value is one that is less than 0.01, according to general consensus. Statistical software in version 22 of SPSS was used to conduct analysis.

RESULT

The total number of diabetic patients were 104 consisting of 45 males and 59 females.

Table 1: Showing FBG, Serum Melatonin and Serum hs-CRP in Type 2 diabetic patients.

	N	Minimum	Maximum	Mean ± SD
Age	104	20	60	42.52 ± 11.60
FBG	104	129	178	148.24 ± 11.14
Melatonin	104	13.74	38.55	23.74 ± 5.34
hs-CRP	104	3.50	8.30	4.62 ± 0.68

Table 2: Pearson Correlation between FBG, Serum Melatonin and Serum hs-CRP.

		FBG mg/dl	Melatonin pg/ml	hs-CRP mg/L
FBG	Pearson Correlation	1	-0.370**	0.347**
	Sig. (2-tailed)		<0.01	<0.01
Melatonin	Pearson Correlation	-0.370**	1	-0.424**
	Sig. (2-tailed)	<0.01		<0.01
hs-CRP	Pearson Correlation	0.347**	-0.424**	1
	Sig. (2-tailed)	<0.01	<0.01	
n		104	104	104

**Correlation is highly significant at the 0.01 level (2-tailed). p-value <0.05. * Correlation is significant at the 0.05 level (2-tailed). p-value. Correlation is no significant at p value >0.05.

DISCUSSION

The pineal gland is the organ that produces and secretes the neuroendocrine hormone melatonin. It primarily maintains the normal “sleep Awakening Cycle” and is responsible for maintaining circadian biological rhythm of the human body [17]. Multiple physiological tissues, including pancreatic islet cells, include melatonin receptors, indicate that melatonin has substantial effects on’ energy expenditure and the

regulation of body weight [18]. Melatonin causes the MT2 receptor to become active, which then limits the release of insulin from pancreatic β-cells and inhibits the second messenger, cGMP. Their activation by melatonin is thought to have a direct impact on the generation of glucagon or insulin, and it offers a biological explanation for how diabetes patients' lower melatonin levels may impact the pancreas' ability to operate [19]. These clinical findings suggest that melatonin enhances blood glucose regulation and that melatonin deficiency may be linked to the onset of T2DM [20].

This study showed that the Fasting Blood Glucose had a significant negative correlation with Serum Melatonin with r and p value (r = - 0.370), (p = <0.01) in patients with T2DM. The presence of a connection between abnormally reduced melatonin levels and diabetes [21,22], suggests that the melatonin signal has a vital function in controlling blood glucose levels and preserving homeostasis [23]. Hence, melatonin has the ability to influence the onset of diabetes by altering the time of insulin production. The disturbance of the daily regulation of insulin release over a 24-hour period is a critical feature of diabetes mellitus [24]. Ramracheya et. al, (2008) have found that elevated glucagon levels in human pancreatic islets due to insulin secretion which is directly stimulates by Melatonin [25].

Similarly, Lauritzen et. al, (2021). suggests that in patients with metabolic disorders, decreases fasting insulin levels and insulin resistance without altering fasting FBG and HbA1c levels by long-term melatonin treatment [26]. People with diabetes have much higher blood levels of inflammatory markers including hs-CRP, IL-6, plasminogen activator inhibitor-1 (PAI-1) and fibrinogen [12]. A recent meta-analysis comprising of twelve studies, all of which were prospective, revealed a correlation between elevated baseline hs-CRP levels and future T2DM insulin resistance, and elevated HbA1c levels [13]. The present study showed that Fasting Blood Glucose had a significant positive correlation with Serum hs-CRP with r and p value (r = 0.388), (p = <0.01) in patients with T2DM.

There may also have a significant relationship between serum hs-CRP and complications of T2DM through the acute phase response [15]. Gohel and Chacko et.al, (2013) showed statistically significant increase in level of hs-CRP in T2DM compared to healthy person [14]. Amanullah S, Jarari A et.al, (2010). conducted a study and found that high levels of serum hs-CRP were significantly associated with age and positively related to insulin resistance. They also concluded that age, BMI, hypersensitivity and body weight has strong association with diabetic individuals [10]. Jichen Zhang, Jiancan Lu, et. al, (2018) suggested that Hyperglycemia causes diabetic complications such as diabetic neuropathy and cognitive impairment by activating nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), one of the major inflammatory signal pathways. NFkB is linked to the generation of proinflammatory cytokines and plays a role in pathological brain inflammation [27]. In this study we found that melatonin level was decreased in diabetic patients and was negatively correlated with hs-CRP with (r = -0.424) and (p = <0.01).

CONCLUSION

A total of 104 diabetic patients of age group 18-60 years were included in this study and their FBG, Serum Melatonin and hs-CRP were analysed. In the present that there is statistically significant negative correlation of Fasting Blood Glucose with Serum Melatonin and positive correlation of FBG with Serum hs-CRP. Serum Melatonin levels

were found to be decreased and Serum hs-CRP levels were found to be increased in T2DM with p-value < 0.001 which is statistically significant. It can be concluded from the present study that there is a correlation between decreased Serum Melatonin and an increased risk for the development of T2DM. The hs-CRP levels are increased in patients who are having Type 2 Diabetes Mellitus which suggests that there is a possible link between Serum hs-CRP and Diabetes.

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