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ORIGINAL ARTICLE

Insulin and Melatonin Modulates the Histo Architecture, Cellular Biochemistry and Receptor Expression During Injury of Hepatic in Diabetic individuals and its treatment

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ABSTRACT

Objective: The purpose of this research was to examine the effects of exogenous melatonin and insulin on the biochemical, serological, histological, and receptor expression architecture of liver tissues in response to hepatic damage.
Study Design: Observational study
Place and Duration: This study was carried out at Hayatabad Medical Complex from November 2021 to March 2022
Methods: Total 72 patients of diabetes mellitus had age 19-78 years were presented in this study. All the patients had hepatic injury and admitted to outpatient department. After obtaining informed written consent detailed demographics of enrolled cases were recorded. Patients received melatonin and insulin therapy and continuous follow up was taken. Outcomes among all patients were recorded in terms of effectiveness. SPSS 23.0 was used to analyze all data.
Results: Mean age of the patients was 42.13±16.42 years and had mean BMI 28.11±8.38 kg/m^2.Most of the patients were from rural areas and were not educated. 45 (62.5%) were married and remaining 27 (37.5%) were not married. Majority patients 50 (69.4%) had diabetes mellitus-2. Other diseases were hypertension, pulmonary disease, respiratory and cardiac disease. As per liver function test, significant increased values were obtained in ALT, AST, ALP, serum cholesterol, LDL, VLD but decrease in HDL level. We found recovery of hepatic injury in 64 (88.9%) cases. Biochemical, cellular structure of liver cells, and the expression pattern of MT1, MT2, and IR receptors were all shown to have significantly recovered and restored.
Conclusion: We concluded in this study that combine therapy of melatonin and insulin among diabetic patients of hepatic injury resulted significantly good results in terms of efficacy and disease recovery.
Keywords: Diabetes Mellitus, Insulin, Melatonin, Efficacy, Hepatic Injury

INTRODUCTION

Obesity is now a serious problem all over the world. One-third of the world's population is now considered overweight or obese [1]. This translates to more than 2 billion individuals. As many other diseases and conditions can be exacerbated by obesity, including type 2 diabetes (T2DM), cholesterol, nonalcoholic fatty liver disorder (NAFLD), and cardiovascular disease [2], the prevalence of obesity and its comorbidities has become increasingly urgent. To halt the spread of obesity, effective measures are thus desperately needed.

Almost every living thing, from simple photosynthetic bacteria to humans, produces the indoleamine hormone melatonin [3]. Melatonin is involved in a wide range of physiological functions. In vertebrates, melatonin is rhythmically generated in the pineal gland under the control of the hypothalamic nucleus of the hypothalamus (SCN) [4], and it exerts potent physiological activities through the melatonin receptors 1 (MT1) and 2 (MT2) [5, 6].

The risk of complications from type 2 diabetes is elevated in people with insulin resistance because of their pro-inflammatory status [6]. Higher secretion rates of inflammatory cytokines such as IL-1, IL-6, and TNF- have been documented in individuals with T2DM, and they have been linked to problems and beta cell abnormalities [7]. Repetition of these studies has shown the central function of IL-1 and TNF- in insulin resistance. Insulin signaling is disrupted and insulin receptor expression is reduced due to TNF- [8]. One of the most important mediators of the inflammation, IL-1, also plays a negative role in blood sugar regulation and beta cell dysfunction [9]. For instance, one study found that enhancing beta-cell secretory activity via blocking the interleukin-1 receptors (IL-1Ra) led to better glycemic control in individuals with type 2 diabetes.

One hormone that plays a role in circadian rhythms is melatonin (N-acetyl-5-methoxytryptamine), which is produced mostly during the night. Retinal light detection during the day inhibits melatonin synthesis, but nighttime light stimulation promotes melatonin production. [10] The pineal gland uses tryptophan as its primary substrate in order to synthesize melatonin. 10 Next to serotonin, 5-hydroxytryptophan is the most common end product of tryptophan metabolism (5-hydroxytryptamine). Aralkylamine N-acetyltransferase (AANAT) converts serotonin to N-acetylserotonin, and N-acetylserotonin O-methyl transferase (ASMT) converts N-acetylserotonin to melatonin in the pineal gland. The endogenous free radical scavenger melatonin has significant antioxidant action. Not only does the pineal gland create melatonin, but so does the liver. AANAT and ASMT were found to be expressed in the liver of goldfish, with the timing of their expression changing in response to changes in illumination. [11] In humans and rats, melatonin regulates a variety of hepatic and gastrointestinal cells by binding to the G protein-coupled receptors MT1 and MT2. These cells include hepatocytes, gallbladder endothelium, and bile duct epithelia. [12,13] Inflammation induced by superoxide anion (ROS) or reactive nitrogen species can lead to oxidative stress, and melatonin can help prevent it. Thus, melatonin treatment is beneficial in a wide range of conditions, including liver ailments. Melatonin's ability to restore circadian rhythms and functions, as well as its reduction of oxidative stress, suggest that it may one day be used in innovative therapies for liver illnesses. [14]

Melatonin was linked to insulin secretion and type 2 diabetes, in addition to its pro properties. According to the literature, there is a correlation between beta cell insulin production, blood sugar, and melatonin production [15].

MATERIAL AND METHODS

This observational study was conducted at Hayatabad Medical Complex from November 2021 to March 2022 and comprised of 72 patients of diabetes. After obtaining informed written consent detailed demographics of enrolled cases were recorded. Patients had history of cardiac surgery, <19 years of age and those did not provide any written consent were excluded from this study.

Patients were aged between 19-78 years. All the patients were admitted to outpatient department. Patients were undergoing for liver function test ALT, AST, ALP, serum cholesterol, LDL, VLD and HDL. Glucose level of all the cases was assessed. Patients received combine therapy of melatonin and insulin. Blood sample of all the cases were taken and sent for laboratory tests. Outcomes among all patients were recorded in terms of effectiveness. SPSS 23.0 was used to analyze all data. Mean standard deviation was used to present baseline details. Frequencies and percentages were used for categorical variables.

RESULTS

Mean age of the patients was 42.13±16.42 years and had mean BMI 28.11±8.38 kg/m^2.Most of the patients were from rural areas and were not educated. 45 (62.5%) were married and remaining 27 (37.5%) were not married. Majority patients 50 (69.4%) had diabetes mellitus-2. 46 (63.9%) cases were smokers. (table-1)

Table-1: Patients with baseline details

Variables	Frequency	Percentage
Mean age (years)	42.13±16.42	
Mean BMI (kg/m^2)	28.11±8.38	
Place of living		
Rural	40	55.6
Urban	32	44.4
Education Status		
Educated	34	52.7
Non-educated	38	47.3
Marital status		
Yes	45	62.5
No	27	37.5
Smokers		
Yes	46	63.9
No	26	36.1
Type of DM		
Type-1	22	30.6
Type-2	50	69.4

Other diseases were hypertension, pulmonary disease, respiratory and cardiac disease. (figure 1)

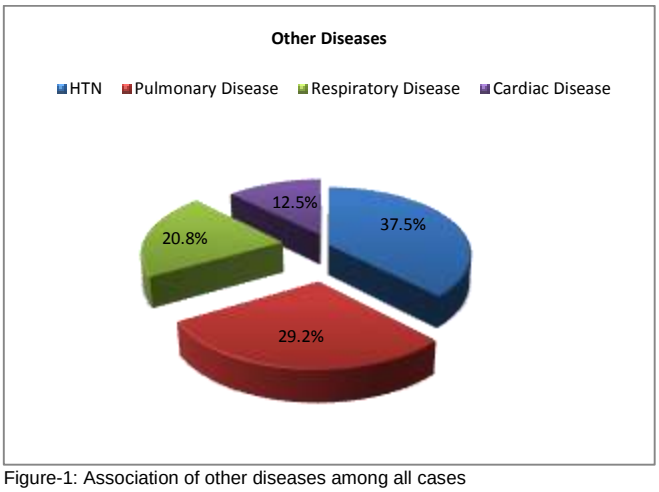

Figure-1: Association of other diseases among all cases

We found significant increased values in ALT, AST, ALP, serum cholesterol, LDL, VLD but decrease in HDL level. (table-2)

Table-2: Outcomes of liver function test

Variables	Mean	Std. Deviation
Alanine aminotransferase U/L	816.6	50.9
Aspartate Aminotransferase U/L	798.16	43.7
alkaline phosphatase U/L	806.3	19.64
serum cholesterol mg/dl	180.17	3.66
LDL mg/dl	98.3	10.88
VLD	86.4	6.97
HDL mg/dl	46.16	3.46

We found recovery of hepatic injury in 64 (88.9%) cases. Biochemical, cellular structure of liver cells, and the expression pattern of MT1, MT2, and IR receptors were all shown to have significantly recovered and restored. (table-3)

Table-3: Efficacy among all cases

Variables	Frequency	Percentage
Effectiveness		
Yes	64	88.9
No	8	11.1

DISCUSSION

The current investigation centered on the effects of co administering melatonin and insulin. Blood glucose levels were found to be significantly elevated in those with diabetes. However, both melatonin and insulin were able to reduce blood glucose levels considerably over the course of a week and on average. Previous findings revealed that melatonin favorably influences on the proliferation/regeneration of -cells and block apoptosis [16], which was clearly corroborated by the results of the current investigation. Antibodies are produced by streptozotocin via a recognized fundamental process. The pancreatic -cell is then attacked by the auto-antibodies. Because of this, pancreatic -cell death occurs, resulting in decreased insulin production and secretion [17].

There is evidence linking pancreatic injury to the onset of diabetes. Reduced insulin production and elevated blood glucose occur when pancreatic islet cells are destroyed [18]. The oxidative stress brought on by high blood sugar levels may be influencing other physiological processes, including the reduction of red blood cell count, haemoglobin glycosylation, and other haematological abnormalities. Melatonin's ability to inhibit -cell damage and speed up their activity has thus been shown. Both melatonin and insulin levels drop in people with diabetes, but this may be corrected with exogenous melatonin and insulin supplementation. This may indicate that protection is afforded by counteracting the stress brought on by diabetes, which in turn reduces the harm done to -cells by oxidative stress and safeguards them from functional overload [19].

One of the most crucial regulators of blood sugar homeostasis in vivo is the hormone glucagon, which acts as an antagonist to insulin. The release of glucagon from pancreatic -cells in response to elevated blood sugar levels increases glucose production by the liver. Multiple processes are activated by the hormone, leading to an increase in blood glucose levels: increased glycogenolysis and gluconeogenesis, and decreased glycogenesis and glycolysis. [19]

Since it was shown that melatonin's influence on insulin was receptor-mediated, it was natural to wonder if it also modulates -cell glucagon secretion. The non - specific melatonin antagonists luzindole and the MT2 receptor-specific antagonists 4P-PDOT were used in incubation studies with TC1.9 cells to show, for the first time, that moonlight mediates its effects on glucagon release via melatonin receptors [20]. Phosphoinositide 3-kinase regulation is another signaling pathway that plays a role in modulating melatonin's actions in pancreatic -cells (PI3K). Founder with the PI3K antagonist wortmannin suppressed the glucagon-increasing impact of melatonin in TC1.9 cells, as shown by incubation tests [20]. Astrocytes, endothelial cells, and even rat pancreatic islets have all been found to respond to melatonin's effects on PI3K, suggesting that this kinase plays a role in melatonin's ability to

control cell growth, differentiation, and survival [21]. It is uncertain whether melatonin similarly affects these characteristics in -cells. Furthermore, cross-talks between both the PLC and PI3K signaling pathways need to be addressed for pancreas -cells, as demonstrated by Batty et al. for glioma cells [22].

Different types of polymorphs, such as neutrophils, eosinophils, and basophils, play important roles in the body's immunological defenses. Since neutrophils are the primary leukocytes and serve as the first line of defense, a drop in their numbers might be hindering their ability to do their job, which in turn slows the healing of wounds. Diabetics have a harder time recovering from wounds, which can lead to more serious complications down the road, such the need for an amputation. This makes diabetes patients extremely vulnerable to any form of infection, which in turn causes a great deal of suffering and death. We found significant increased values in ALT, AST, ALP, serum cholesterol, LDL, VLD but decrease in HDL level [23]

CONCLUSION

We concluded in this study that combine therapy of melatonin and insulin among diabetic patients of hepatic injury resulted significantly good results in terms of efficacy and disease recovery.

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