Int J Pharm Bio Sci 2015 July; 6(3): (B) 295 - 300

**Research Article** **Biochemistry**

**International Journal of Pharma and Bio Sciences** **ISSN 0975-6299**

# CORRELATION WITH SERUM MELATONIN LEVELS TO THE PREVALENCE OF TYPE II DIABETES MELLITUS IN BORN BLIND SUBJECTS

**PROF.DR.N.N.ANAND[1*] AND PROF.DR.V.PADMA[2]**

*[1.] Professor of Medicine,SreeBalaji Medical College, BALDORC Bharath University, Chrompet, Chennai ,India*
*[2.] Professor of Medicine,SreeBalaji Medical College, BALDORC, Bharath University, Chrompet,Chennai*

## ABSTRACT

Born Blind subjects are able to lead a near normal life with a little percentage of chronic ailments like Diabetes Mellitus, Hypertension, Renal disease and Cardio Vascular problems. To detect the prevalence of T2DM in Born Blind subjects and to find out the prevalence of metabolic syndrome .To find out the levels of melatonin in born blind subjects . 500 born blind subjects were recruited in and around Chennai. Participants were within 30-60 years. Both sexes are included. Among 500participants , 404 males and 96 females. 210(42)blind people had abnormal waist hip ratio. A high level of Serum Melatonin level was observed among them at 38.5±0.6. The Prevalence of Prediabetes was 11(2.2) , hypertension to be among 19(3.8) and a negligible case of 1(0.2) with both conditions. Average HbA1C was 5.9. Higher melatonin secretion was associated with a lower risk of developing T2DM.

**KEY WORDS: melatonin, diabetes mellitus, born blind.**

**PROF.DR.N.N.ANAND**
**Professor of Medicine,SreeBalaji Medical College,**
**BALDORC Bharath University, Chrompet, Chennai ,India**

*Corresponding author

# INTRODUCTION

Born Blind subjects lead a near normal life with a little percentage of chronic ailments like Hypertension, Renal disease ,diabetes and Cardio Vascular problems.Rarely they suffer from Diabetes mellitus. This reality prompted us to investigate these Blind subjects to assess the prevalence of Type II Diabetes Mellitus (T2DM) and other Metabolic Syndrome.

### *AIM*

To detect the prevalence of T2DM in Born Blind subjects.

To correlate with serum melatonin, waist, hip ratio, systolic and diastolic Blood Pressure and HbA1C levels..

# MATERIALS AND METHODS

500 Blind subjects were recruited from Chennai. All of them were born blind. None of them were taking any drugs like hormonal drugs, steroids,Anti Diabetic,Anti Hypertensive, Anti Depressant drugs.Subjects who became blind later in life due to any illness were excluded from the study. Majority of subjects belongs to lower socio economic groups. None of them had any metabolic disorders.All participants were within the age group of 30-60 years. Both sexes were included. Among 500 participants , 404were males and 96 were females.. After getting an informed consent these subjects were investigated:blood pressure , fasting blood sugar,post prandial blood sugar, HbA1C and serum melatonin (early morning sample obtained around 04:30 a.m.) were done.

### *Assay technique*

BG MLT ELISA KIT was used for quantitative determination of serum melatonin. By using quantitative sandwich enzyme immune assay technique the melatonin levels were estimated.

# RESULTS

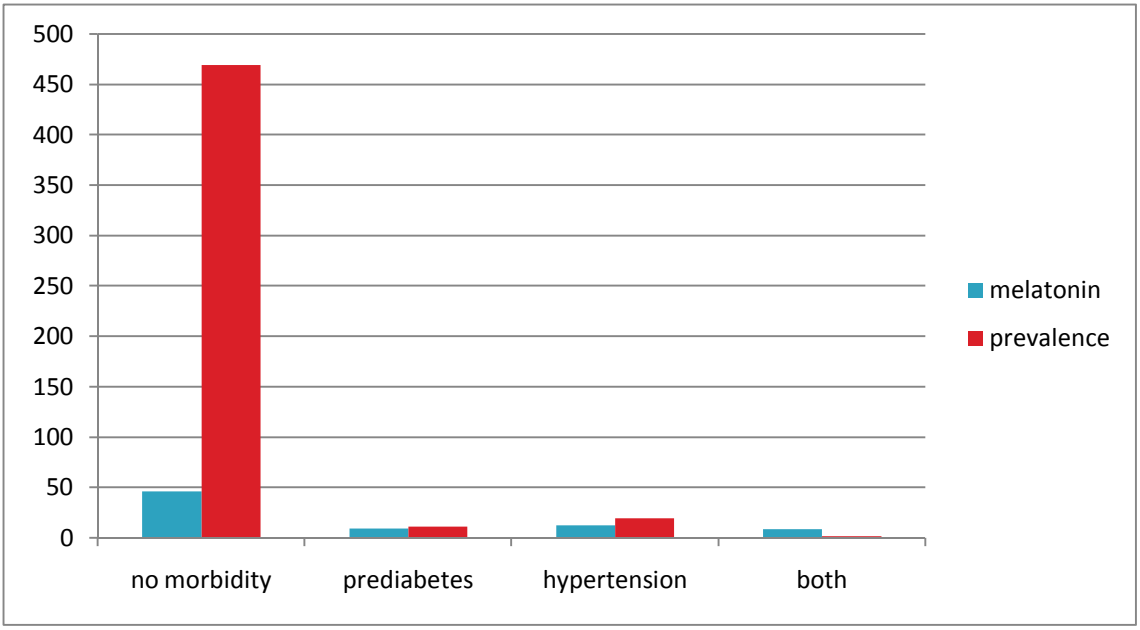
The information collected from 500 participants was analysed using SPSS 15.0 and the Descriptive statistics for the Qualitative and Quantitative parameters are presented in Table 1 and Table 2. Chi-square test used to find the association between Morbidity and Serum Melatonin abnormality with a 5% level of Significance.

**Table 1**
***Analysis of variables***

| VARIABLES | | N (%) |
|---|---|---|
| 1. | Age (years) | |
| | 31-40 | 222 (44.4) |
| | 41-50 | 148 (29.6) |
| | 51-60 | 130 (26) |
| 2. | Sex | |
| | Male | 404 (80.8) |
| | Female | 96 (19.2) |
| 3. | Waist Hip Ratio | |
| | < 1 | |
| | ≥ 1 | |
| 4. | Systolic BP (mmHg) | 290 (58) |
| | < 140 | 210 (42) |
| | ≥ 140 | |
| 5. | Diastolic BP (mmHg) | 408 (81.7) |
| | < 90 | 92 (18.3) |
| | ≥ 90 | |
| 6. | Fasting BS(mg%) | 368 (73.8) |
| | < 110 | 132 (26.2) |
| | 110 - 120 | |
| 7. | PostProndialBS(mg%) | 476 (95.2) |
| | < 140 | 24 ( 4.8) |
| | 140 - 160 | |
| 8. | Serum Melatonin Level | 457 (91.5) |
| | < 15 pg | 43 ( 8.5) |
| | ≥ 15 pg | |
| 9. | Morbidity | 18 ( 3.6) |
| | Nil | 482 (96.4) |
| | Prediabetes | |
| | Diabetes & Hypertension | 452 (90.5) |
| | Hypertension | 18 ( 3.6) |
| | | 1 ( 0.2) |
| | | 29 ( 5.8) |

In the present study majority 404 (80.8) of them were males compared to 96(19.2) females . 344(68.4) had an abnormal waist hip ratio. Mean±SE(Mean) of the SBP/DBP were observed to be 125.3±0.6 / 80.3±0.4 and that of the Fasting glucose as 93.8±0.6 with a post prondial 139.7±0.9. A high level of Serum Melatonin level was observed among them as 38.5±0.6. The Prevalence of Prediabetes was 18(3.6) , hypertension to be among 29(5.8) and a negligible case of 1(0.2) with both hypertension and diabetes.

**Figure 1**
***Serum Melatonin Level In 500 subjects***




***This figure shows a significant increase in serum melatonin levels of 46 in 469 subjects.11 had prediabetes with a lower serum melatonin of 9,19 had hypertension with a melatonin level of 12 and 1 had both prediabetes and hypertension with a melatonin level of 8pg/ml.The mean normal level of serum melatonin is 6.7-8.6 pg/ml.***

Middle aged subjects were recruited as they were prone for diabetic and metabolic syndrome, which will be always high. Our study revealed systolic hypertension was seen in around 18.3 % and diastolic hypertension in 26.2%. In normal vision subjects, with same age group and waist hip ratio ,many studies showed prevalence of T2DM to be around 70%, whereas in this study none of them were having frank diabetes,around 2% were having pre diabetic range of blood sugars. 96.4% people were having higher levels of serum melatonin levels (more than 15 pg). Only 3.6% levels had low levels of melatonin (less than 5 pg) and also had a prediabetic range of blood sugar.

## DISCUSSION

Melatonin is a circulating hormone that is mainly released from the pineal gland. It is best known as a regulator of seasonal and circadian rhythms, its levels being high during the night and low during the day. Interestingly, insulin levels have also adapted to day/night changes through melatonin-dependent synchronization. This regulation may be explained by the inhibiting action of melatonin on insulin release, which is transmitted through both the pertussis-toxin-sensitive membrane receptors MT1 and MT2 and the second messengers 3',5'-cyclic adenosine monophosphate, 3',5'-cyclic guanosine monophosphate and inositol 1,4,5-trisphosphate[1]. Melatonin may influence diabetes and associated metabolic disturbances not only by regulating insulin secretion, but also by providing protection against reactive oxygen species, since pancreatic β-cells are very susceptible to oxidative stress because they possess only low-antioxidative capacity. On the other hand, in several genetic association studies, single nucleotide polymorphysms of the human MT2 receptor have been described as being causally linked to an elevated risk of

developing type 2 diabetes. This suggests that these individuals may be more sensitive to the actions of melatonin, thereby leading to impaired insulin secretion. Melatonin produced by Pineal gland is termed as an endogenous clock hormone. This hormone is one of the most reliable markers of the body clock hormone

### *Melatonin and glucose homeostasis*

### *Circulating insulin and melatonin levels*

Nocturnal levels of the anabolic hormone insulin are low since humans are programmed not to eat during the night, there will be little need for insulin, which controls metabolism in the postprandial and anabolic states. In fact, an excess of insulin could have detrimental effects on the central nervous system if hypoglycaemia were to occur. Because melatonin is a biological signal of darkness and, consequently, reduced metabolism, it has been proposed that melatonin could contribute to the nocturnal lowering of insulin in humans. That insulin secretion is controlled by circadian mechanisms is supported by studies of humans with circadian misalignment, who are reported to show profound perturbations of plasma glucose and insulin levels. The concept is supported by the assumption that there is a circadian clock in pancreatic islets.There are indications that the diurnal secretion of melatonin is altered in diabetes, particularly when neuropathy is evident. Peschke[2]reported reduced circulating levels of melatonin and elevated levels of insulin in type 2 diabetic patients, with a statistically significant negative correlation found between the two. No information on treatment or disease duration was given in this study[2], but the increased levels of insulin suggest that the patients did not suffer from advanced insulin-requiring type 2 diabetes. Similarly, nocturnal melatonin levels are reduced in the GotoKakizaki (GK) rat, a model of type 2 diabetes.

### *Melatonin receptors in pancreatic islets and beta cells*

If melatonin has direct effects on insulin secretion, its receptors should be present in islets of Langerhans, preferably beta cells. This indeed appears to be the case, as inferred from studies using the non-hydrolysable GTP analogue guanosine 5′-O-(3-thiotriphosphate) and the melatonin antagonist luzindole[3], both of which block the effects of melatonin on insulin secretion from neonatal rat islets. MTNR1A mRNA was subsequently demonstrated in INS-1 cells in human islets. MTNR1B mRNA has also been detected in rat and human islets[4], but at levels several-fold lower than those of MTNR1A mRNA. MIN-6 cells also express both forms of the receptor. In human islets, MTNR1A mRNA occurs primarily in alpha cells[4], and the level of MTNR1B mRNA is lower than that of MTNR1A mRNA.MTNR1B protein predominantly occurs in beta cells in either human or rodent islets; MTNR1A protein is found in peripherally located beta cells. Insulin secretion in pancreatic β-cells is organized by a circadian rhythm In this case, insulin and melatonin plasma concentrations change in an opposing manner during the 24-h period, i.e., melatonin peaks when insulin is at a low level, and vice versa. Melatonin stimulates the release of glucagon from perifused human islets[4]; the insulin release was also stimulated, presumably indirectly through glucagon. The inhibitory effects of melatonin on insulin secretion have been replicated in clonal beta cells.

### *Effects of insulin on melatonin*

It has been argued that insulin itself controls the production and subsequent release of melatonin. This argument is difficult to resolve, given the many effects induced by insulin, which secondarily may affect the pineal gland. The concept is supported by the finding of Ins mRNA in the pineal gland. Indeed, both glucose and insulin reduce adrenaline (epinephrine)-induced melatonin secretion from perifused pineal glands[5]. Although it is likely that the pineal gland is exposed to circulating insulin, given that it is localised outside the blood–brain barrier the identity of the cells that harbour the insulin receptor has not yet been determined.

### *Genome-wide association studies and MTNR1B*

In view of the effects of melatonin on islets and on whole body metabolism, a link between melatonin receptors and type 2 diabetes was suggested[6] following the demonstration of increased levels of MTNR1A and MTNR1B mRNA in pancreatic tissue from

patients with type 2 diabetes and increased immunolabelling of MTNR1A and MTNR1B. Although these results were qualitative rather than quantitative, it was postulated that there is a link between the melatonin system and the pathogenesis of the disease. While an association between MTNR1A and type 2diabetes has not been confirmed in the recently performed genome-wide association studies[7] there is now strong support for associations of genetic variation in the MTNR1B locus with fasting glucose levels, insulin secretion and type 2diabetes. In fact, two different single nucleotide polymorphisms (SNPs; rs1387153 and rs10830963) in MTNR1B were reported to be associated with type 2 diabetes, and there appear to be additional SNPs in this gene that show a similar association[7]. Although rs10830963 maps to within the single 11.5 kb intron of MTNR1B, it does not interfere with the binding of consensus transcription factors or with splicing. Thus, it is likely that the SNPs reported to be associated with MTNR1B tag the same signal. Very recently, associations of rs10830963 with elevated fasting plasma glucose and future risk of type 2 diabetes was confirmed in a Chinese population. All recently published articles on the variation in MTNR1B report an association with elevated fasting plasma glucose. This appears to be accounted for by impaired beta cell function. Deterioration of glucose-stimulated insulin secretion over time in carriers of the risk allele was reported in the Botnia prospective study. Moreover, reports find that variations in MTNR1B are associated with or predict future type 2 diabetes with an odds ratio ranging between 1.09 and 1.20. This may seem a modest increase in risk, but it is, in fact, of a similar magnitude to those previously reported for other genes associated with an increased risk of type 2 diabetes. It emphasises that common type 2 diabetes is a polygenic disease, whereby each gene makes a variable, often small, contribution to the overall risk. Indeed, it has been shown that carriers of several risk variants are subject to an additive risk of developing the disease. Moreover, the risk allele of MTNR1B appears to be relatively unique among genes affecting fasting plasma glucose in that it also is significantly associated with future risk of type 2 diabetes most of the previously described candidate genes for type 2 diabetes do not affect fasting plasma glucose, once people with subclinical diabetes are excluded from the analysis. It is found that both MTNR1B mRNA and the protein occur in human islets, predominantly beta cells. This was confirmed by the finding that sorted human beta cells and islets contain identical mRNA species. Clearly, the SNPs in MTNR1B that are associated with, for example, type 2 diabetes, may in themselves not be pathogenic, but, rather, serve as markers for an allele linked to the disease. However, levels of MTNR1B mRNA in islets from carriers of a GG genotype are higher in individuals older than 45 years, and a trend for increased levels of the receptor mRNA in islets from type 2 diabetic patients is also evident. This strongly suggests that MTNR1B is responsible for the increased risk of type 2 diabetes in carriers of the risk allele. Ongoing sequencing of MTNR1B will hopefully reveal pathogenic sequence alterations.

### *Pathogenetic implications of the association between MTNR1B and type 2 diabetes*

Alterations in MTNR1B are, beyond doubt, linked to an increased risk of type 2 diabetes[7] the level of statistical significance is very high but the precise nature of the link remains to be clarified. The work performed to date does provide some clues. Levels of MTNR1B mRNA are increased in older carriers of the risk allele. Given that most of the available data support a direct inhibitory effect of melatonin on insulin secretion, an at risk individual may thus be more sensitive to the inhibitory effect of melatonin than an individual without the risk allele, who would have a normal islet level of MTNR1B. Such a restraining effect of melatonin is in line with the impairment of early phase insulin secretion and reduced HOMA-B observed in carriers of the risk allele.

## CONCLUSION

Previous studies have revealed that innormal vision people with diabetes melatonin level was low. In the present study, 96.4% people were having higher level of serum melatonin levels (more than15 pg). Melatonin plays a vital role in preventing the diabetes, probably by means of insulin secretion and

sensitization, through melatonin receptor 1B also known as MT2 Higher melatonin secretion were associated with a lower risk of developing T2DM. Further research is warranted to assess whether melatonin estimation will be an useful tool to detect the diabetes in the early stage in general population.

## REFERENCES


1. Axelrod J, Weissbach H. Enzymatic O-methylation of N-acetylserotonin to melatonin. Science, 131:1312-3,(1960).
2. Peschke E, Frese T, Chankiewitz E Diabetic GotoKakizaki rats as well as type 2 diabetic patients show a decreased diurnal serum melatonin level and an increased pancreatic melatonin-receptor status. J Pineal Res 40:135–143(2006).
3. Peschke E, Fauteck JD, Musshoff U, Schmidt F, Beckmann A, Peschke D . Evidence for a melatonin receptor within pancreatic islets of neonate rats: functional, autoradiographic, and molecular investigations. J Pineal Res, 28:156–164(2000).
4. Ramracheya RD, Muller DS, Squires PE .Function and expression of melatonin receptors on human pancreatic islets. J Pineal Res, 44:273–279(2008).
5. Peschke E, Wolgast S, Bazwinsky I, Ponicke K, Muhlbauer E . Increased melatonin synthesis in pineal glands of rats in streptozotocin induced type 1 diabetes. J Pineal Res. 45:439–448(2008).
6. Peschke E, Stumpf I, Bazwinsky I, Litvak L, Dralle H, Muhlbauer E. Melatonin and type 2 diabetes—a possible link? J Pineal Res, 42:350–358(2007).
7. Prokopenko I, Langenberg C, FlorezJC . Variants in MTNR1B influence fasting glucose levels. Nat Genet, 41:77–81(2009).