The Impact of Melatonin on Glucose Homeostasis

Melatonin ve Glukoz Metabolizması Üzerine Etkisi

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Abstract

Objective: Melatonin is a pineal product mainly charged with the maintenance of antioxidant conditions in human. This study is performed to identify the short-term effect of melatonin on glucose homeostasis in diabetic patients.

Materials and Methods: Melatonin and placebo were given perorally to sixty patients. Blood glucose and insulin levels were measured with constant intervals.

Results: No significant correlation was found among the levels of glucose, insulin and HOMA-IR index at any time after melatonin/placebo administration.

Conclusions: Prospective studies with long-term use of melatonin are needed to define the exact role of melatonin in glucose homeostasis. *Turk Jem 2009; 13: 52-5*

Key words: Melatonin, glucose, insulin, diabetes mellitus, insulin resistance

Özet

Amaç: Melatonin pineal bezden salınan ve antioksidan olarak görev yapan bir hormondur. Bu çalışma diabetik hastalarda melatoninin glukoz dengesi üzerine etkisini irdelemek adına planlandı.

Gereç ve Yöntemler: Toplam 60 hastaya melatonin ve plasebo dönüşümlü olarak oral yolla uygulandı. Belirli aralıklarla kan glukoz ve insülin düzeyleri ölçüldü.

Bulgular: Melatonin/plasebo uygulamasından sonra herhangi bir zamanda ölçülen glukoz, insülin düzeyleri ve HOMA-IR indeksleri arasında anlamlı korelasyon saptanmadı.

Sonuç: Melatoninin glukoz dengesi üzerine olan etkisinin ileriye dönük çalışmalarla gösterilmesi gerekmektedir. *Türk Jem 2009; 13: 52-5*

Anahtar kelimeler: Melatonin, glukoz, insülin, diabetes mellitus, insülin direnci

Introduction

Melatonin (N-acetyl-5-methoxytryptamine) is a pineal product which is mainly synthesized and secreted during the dark phase of the diurnal environmental light-dark cycle (1-13). As melatonin acts like an internal synchronizer, the wide range of its essential physiological functions includes regulation of the circadian rhythm and blood pressure, oncogenesis, retinal physiology, seasonal reproduction of animals, ovarian functions and osteoblast differentiation (2,5,8,12). No physiological barriers have been identified for melatonin due to its lipophylic structure. It is also claimed that melatonin plays a role in the protection of the tissues against oxidative stress and free radical damage, which makes it an endogenous antioxidant molecule through its free radical scavenging properties (1,2,4,5,7,10,14-22). Melatonin regulates gene expressions and activities of the antioxidant and prooxidant enzymes (1,7). In vivo and in vitro experimental studies have demonstrated that melatonin can prevent the toxic effects of reactive oxygen radicals (4,5). The cumulative oxidative stress has an important role in the pathogenesis of long-term diabetic complications regarding the relationship between oxidative tissue injury and diabetes. Melatonin may reduce the risk of diabetic complications due to its antioxidant profile.

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Glucose homeostasis depends on the balance between glucose delivery and glucose utilization. Glycemia and insulinemia have a distinct diurnal rhythm unrelated to blood glucose concentration and insulin secretion. However, the exact role of pineal gland and its main secretory product, melatonin, in the process of glucose and insulin metabolism has not been determined yet. The pineal gland regulates glucose homeostasis, particularly by its effect on the insulin secretion from pancreatic B cells. It is established that melatonin shows its anti-glucose effect directly through the receptors on hepatocytes and pancreatic B cells (6,22,23). It is indicated that pinealectomy causes a decrease in hepatic and muscular glucogenesis which provides an increase in the blood levels of glucose and a decrease in insulin, while it may be responsible for glucose intolerance and impaired insulin secretion as well.

This study is performed to identify the short-term effects of melatonin on blood glucose and insulin levels in type 2 diabetic patients.

Materials and Methods

Study population

Sixty patients with type 2 diabetes mellitus were enrolled in the study. The study population was divided into three groups; premenopausal women (I. group), postmenopausal women (II. group), and men (III. group), each of which consisted of 20 patients. All the patients were treated with diet±oral antidiabetics and none of them were on insulin. Pregnancy, depression or autoimmune conditions were exclusion criteria. Complete blood counts, hepatic and renal tests were within normal limits. All the patients gave their informed consent to participate in the study.

Study design

Following a 10-hour fast, each patient was admitted to the hospital at 08:00 am and kept at rest. Each patient received oral melatonin (3 mg) and oral placebo on the first and second days, respectively. The patients did not use oral antidiabetics during the study period. Blood samples were taken at 0, 60, 120 and 180 minutes following melatonin/placebo administration, and blood glucose and insulin levels were measured at the time intervals, as mentioned above. HOMA-IR index, which is known to be the indicator of the insulin resistance, was calculated at 0 and 180 minutes after melatonin/placebo administration according to the following formula (HOMA-IR index: [plasma glucose (mmol/lt) x insulin (μu/ml)] /22.5). Blood glucose levels were measured using Hexokinase (Abbott) method on Aeroset autoanalyzer. Insulin levels were measured using Radioimmunoassay (RIA) method and DPC kit.

Statistical analysis

The differences between the groups were analyzed by Mann-Whitney U test, Chi-Square test, Wilcoxon test, Friedman test and Kruskal-Wallis variance analysis. The relations between variables were evaluated with Pearson or Sperman correlation tests. Analysis of the data was performed using SPSS for Windows V. 10.0 (SPSS Inc., Chicago, IL, USA). A value of $p<0.05$ was considered to represent a statistically significant difference.

Result

The study cohort was divided into three groups; premenopausal women, postmenopausal women, and men, each of which consisted of 20 patients. The median age was 44.5 (38-53), 57.3 (40-70) and 55 (34-74) years in the I., II. and III. group, respectively. The mean HbA1c level was 7.53±1.66, 7.09±1.08 and 7.6±1.59 for I., II. and III. group, respectively. Blood glucose and insulin levels were measured at 0, 60, 120 and 180 minutes following melatonin/placebo administration and HOMA-IR index was calculated for each group at 0 and 180 minutes after melatonin/placebo. The mean values of glucose-insulin levels and HOMA-IR index are shown on Table 1.

Age (p=0.02), comorbid diseases (p=0.001) and creatinine levels (p=0.005) were statistically different among the three groups of patients. The body mass index, disease duration, hemoglobin,

Table 1. The mean values of glucose, insulin and HOMA-IR index in the three groups after administration of melatonin (M) and placebo (P)

	Premenopausal women (n=20) mean±SD	Postmenopausal women (n=20) mean±SD	Men (n=20) mean±SD
Glucose (0')/M (mg/dl)	152.65±47.85	140.75±45.07	130.85±26.00
Glucose (60')/M (mg/dl)	154.95±50.89	143.35±49.61	135.85±27.62
Glucose (120')/M (mg/dl)	148.05±48.60	143.55±48.22	134.65±26.32
Glucose (180')/M (mg/dl)	139.05±45.25	139.00±47.38	126.45±21.98
Glucose (0')/P (mg/dl)	153.75±52.90	152.25±47,09	130.10±28.44
Glucose (60')/P (mg/dl)	155.10±51.76	148.30±48,43	130.70±28.61
Glucose (120')/P (mg/dl)	145.50±48.59	143.45±47.09	131.35±27.95
Glucose (180')/P (mg/dl)	139.65±45.72	139.55±44.84	124.85±24.46
Insulin (0')/M (IU/ml)	9.82±4.42	9.19±6.22	10.6±5.36
Insulin (60')/M (IU/ml)	12.89±8.93	9.18±6.82	13.09±12.62
Insulin (120')/M (IU/ml)	10.71±7.40	9.65±6.44	10.52±6.14
Insulin (180')/M (IU/ml)	11.41±6.65	10.52±7.32	10.11±6.37
Insulin (0')/P (IU/ml)	13.72±19.06	10.85±6.11	12.28±11.17
Insulin (60')/P (IU/ml)	13.06±9.64	10.13±7.65	11.42±7.59
Insulin (120')/P (IU/ml)	11.96±9.03	9.52±4.88	11.67±9.56
Insulin (180')/P (IU/ml)	9.68±7.49	9.84±5.14	11.30±7.74
Homa-IR (0')/M	3.72±2.31	3.32±3.03	3.46±2.00
Homa-IR (180')/M	4.23±3.27	3.66±3.22	3.14±2.30
Homa-IR (0')/P	6.54±14.20	4.23±3.08	3.9±3.62
Homa-IR (180')/P	3.68±4.68	3.35±2.26	3.56±2.86

white blood cell count, platelet count, blood urea nitrogen, sodium, calcium, uric acid, aspartate transaminase, alanine transaminase, alkaline phosphatase, gamma-glutamyltransferase, direct/indirect bilirubin, albumin, total cholesterol, low density lipoprotein (LDL), high density lipoprotein (HDL), very low density lipoprotein (VLDL), triglyceride, HbA1c, fructosamine, and proteinuria were not statistically different among the three groups ($p>0.05$).

There was a positive correlation between the duration of diabetes and body mass index in the premenopausal ($r=0.53$, $p=0.01$) and postmenopausal groups ($r=0.49$, $p=0.02$). There was a positive correlation between HbA1c and fructosamine levels in all three groups; premenopausal ($r=0.90$, $p<0.001$), postmenopausal ($r=0.71$, $p<0.001$), and men ($r=0.58$, $p=0.007$), respectively.

In the analysis of temporal changes in blood glucose, insulin and HOMA-IR index, only the temporal decrease in glucose level after the administration of both melatonin and placebo was found to be statistically significant in the premenopausal ($p<0.001$, $p<0.001$), postmenopausal ($p<0.05$, $p<0.05$), and men group ($p<0.05$, $p<0.05$), respectively. The temporal alteration of insulin levels and HOMA-IR index after melatonin/placebo administration was statistically insignificant in three groups ($p>0.05$).

There was no relationship among the levels of glucose, insulin and HOMA-IR index at any time among all three study arms.

Discussion

Melatonin, the chief secretory product of the pineal gland, has many physiological functions, including regulation of the circadian rhythm (24). The studies dealing with the physiological role of melatonin have mainly focused on oxidative stress, dyslipidemia and glucose metabolism. As the majority of the previous studies were performed on animal models, our data remains insufficient for understanding the essential role of melatonin in human physiology. The results of the studies were found to be controversial in humans and rats, which means that the physiological role and function of melatonin may be different in animals and men. Melatonin regulates the 24-hour mean glucose concentration by directly acting on hepatocytes and pancreatic B cells in rats. Pinealectomy prevents the nocturnal decrease in plasma glucose concentration which results in an increased 24-hour mean glucose concentration in rats. Even if the mean insulin concentration remains constant, the sensitivity to insulin has been shown to be decreased as expected (6).

The pineal gland maintains the glucose homeostasis and insulin secretion from the pancreatic B cells (6,22,23). Pinealectomy reduces the glucose tolerance in rats by preventing the hepatic and muscular glucogenesis resulting in increased insulin resistance (6,25,26). It is demonstrated that the plasma glucose level has a diurnal rhythm in rats, which depends on the circadian secretion of melatonin or the control mechanism of suprachiasmatic nucleus on hepatic glucose delivery (6,13). Melatonin increases the insulin sensitivity of the peripheral tissues, thus insulin sensitivity and gene expression of GLUT 4 are decreased in melatonin deficiency in pinealectomized rats (13,26).

In animal studies, it is demonstrated that the diurnal variation of blood glucose concentration is related to the circadian rhythm of melatonin, which increases the activity of insulin in the insulin-sensitive tissues, effects the secretion of glucagon, regulates the glucose delivery of hepatocytes and reduces the insulin resistance (6,26). Melatonin acts as a free radical scavenger and reduces hyperglycemia, oxidative stress and lipid peroxidation, the primary processes underlying the pathogenesis of the long-term diabetic complications (5,7,12).

Cagnacci et al examined the effect of melatonin on glucose metabolism in 22 postmenopausal women. They suggested that 1 mg/day melatonin reduces glucose tolerance and insulin sensitivity (17). As the dosage of melatonin is lower than its normal plasma levels, it may not be accurate to evaluate its potential effect with suboptimal plasma levels. The study population reflects a small proportion of patients in which the role of gonadal steroids is probably underestimated.

In the current study, we showed no significant difference in blood glucose and insulin levels after melatonin or placebo administration in premenopausal women, postmenopausal women, and men. As oral antidiabetics were withdrawn 24 hours before the onset of the study, the ongoing hypoglycemic effects of the drugs could have a contributory role. Nevertheless, the effect of psychological factors might have surpassing effects as the results of the melatonin and placebo groups were similar.

Based on the results of this study, indicating no difference between melatonin and placebo groups, melatonin may not have an effect on glucose and insulin levels in diabetic men and women, in contrast to animal studies. On the other hand, melatonin exposure during night with convenience to its physiological secretion period may intensify its functional effects on glucose homeostasis.

We conclude that short-term administration of melatonin seems not to influence the glucose and insulin levels in human. Prospective studies with long-term and appropriate use of melatonin at proper doses in diabetics would allow us to learn more about the antioxidant profile of melatonin and its protective effects on diabetic complications.

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