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EFFECT OF MELATONIN SUPPLEMENTATION AND TYPE 2 DIABETES MELLITUS (T2DM) : A SYSTEMATIC REVIEW

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Abstract
Pineal gland secretion of the endogenous indole amine known as melatonin is regulated by the hypothalamus. The 24-hour cycle of circadian rhythms is partially responsible for the timing of physiologic processes. Research conducted in the past has demonstrated that melatonin possesses a variety of advantageous properties, such as activities that limit the responses of adrenocorticotropic hormones and good effects that have an effect on metabolic profiles. In addition, there has been research carried out on animals, in addition to certain human trials that were not randomized, which have suggested that the use of melatonin may have a positive influence on improving glycemic control, insulin resistance, hypertension, and dyslipidemia. These studies were carried out in conjunction with one another. In studies conducted on both humans and animals, melatonin was discovered to have a beneficial effect on the regulation of blood glucose levels. The expression of the glucose transporter type 4 (GLUT4) gene is reduced in mice that have had their pineal glands surgically removed, which leads to glucose intolerance and insulin resistance. Melatonin treatment is effective in reducing the severity of these symptoms. Melatonin's anti-oxidative activity effectively lowers oxidative stress, which is a significant contributor to the progression of a wide variety of problems that can arise from diseases such as diabetes.

Keyword: *Diabetes Mellitus; Hyperglycemia; Melatonin; Oxidative Stress*

INTRODUCTION

Hyperglycemia, which can be caused by insulin resistance or a decrease in insulin production, is the defining feature of diabetes mellitus (DM), a metabolic condition that affects people all over the world and frequently poses a threat to their lives. Diabetes mellitus has become more widespread in recent decades.[1] The International Diabetes Mellitus Federation estimates that 592 million people will have diabetes mellitus by 2035, making it one of the leading causes of death worldwide.[2,3]According to the findings of a number of studies, diabetes mellitus has the potential to play a role in the development of a wide range of complications. These complications include diabetic cardiovascular complications, diabetic neuropathy, retinopathy, nephropathy, and liver complications. These are the most common causes of morbidity and mortality associated with the disease. As a consequence of this, it is of the utmost importance to search for efficient methods of controlling diabetes mellitus and preventing the complications that it can cause.[4,5]Pineal hormone has recently been shown to have an effect on insulin secretion, carbohydrate metabolism, and blood glucose levels.[6] Melatonin (N-acetyl-5-methoxytryptamine), an endocrine agent derived from tryptophan, is primarily synthesized by the pineal gland and locally by a variety of other tissues. Diabetes mellitus is associated with lower serum melatonin concentrations in diabetic GotoKakizaki rats, despite higher insulin levels in diabetic subjects. Melatonin also has anti-aging, anti-inflammatory, antioxidant, and antihypertensive properties.[7]Melatonin is an endogenous indole amine that is released by the pineal gland. It plays a role in physiologic timings that are determined by circadian rhythms. In the past, research has shown that melatonin has a number of favorable benefits, including inhibitory activities on adrenocorticotropic hormone responses as well as positive impacts on metabolic profiles. In addition, research conducted on animals as well as certain human trials that were not randomized have suggested that the administration of melatonin may have a positive influence on improving glycemic control, insulin resistance, hypertension, and dyslipidemia.[8]Intake of melatonin has been shown to regulate blood glucose levels because of its ability to bind directly to melatonin receptors on hepatocytes. Additionally, melatonin intake has been shown to regulate the uptake of glucose in adipocytes by modulating the expression of the glucose uptake transporter.[9] In addition, it has been demonstrated that melatonin can enhance the release of glucagon, which is another hormone that plays a significant role in the metabolism of glucose and insulin.[10] This article investigate the association between melatonin supplement and type 2 diabetes mellitus.

METHODS

Protocol

The Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 checklist served as the basis for the regulations that guided the execution of this systematic review.

Eligibility Criteria

This systematic review was developed to analyze papers on "melatonin supplementation" and "type 2 diabetes mellitus". These are the topics that were extensively covered in the study that was considered. In order for your work to be considered, the following conditions must be met: 1) Articles must be written in the English language. 2) Articles must have been published after 2017, but prior to the creation of this systematic review. Under no circumstances will the following types of textual contributions be considered for inclusion in the anthology: 1) Editorial letters, 2) submissions without a Digital Object Identifier (DOI), and 3) article reviews and submissions similar to those previously published in the journal.

Search Strategy

The search for studies to be included in the systematic review was carried out from December, 2nd 2022 using the PubMed and SagePub databases by inputting the words: "melatonin supplementation" and "type 2 diabetes mellitus". Where *("melatonin"[MeSH Terms] OR "melatonin"[All Fields] OR "melatonin s"[All Fields] OR "melatonine"[All Fields] OR "melatonins"[All Fields]) AND ("supplemental"[All Fields] OR "supplementating"[All Fields] OR "supplementation"[All Fields] OR "supplementation s"[All Fields] OR "supplementations"[All Fields] OR "supplemention"[All Fields]) AND ("diabetes mellitus, type 2"[MeSH Terms] OR "type 2 diabetes mellitus"[All Fields])* is used as search keywords.

Data retrieval

The author of the study revised the criteria for what should be included in the study and what should not be included in the study after conducting a literature review and reading the titles and abstracts of previously published studies. This was done in order to determine what should be included in the study and what should not be included in the study. After reviewing prior research that had been published, the author decided to make these adjustments.

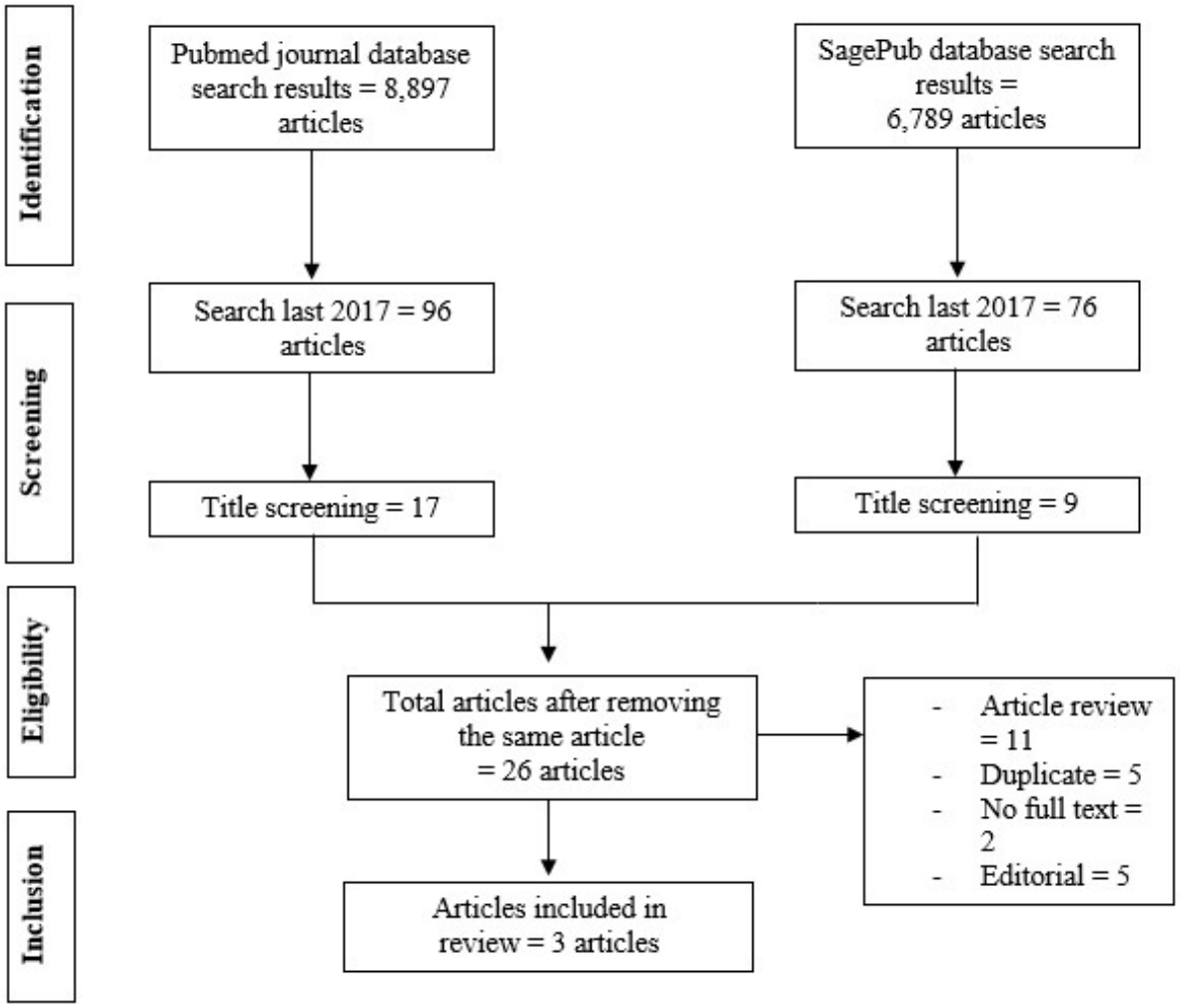

Figure 1. Article search flowchart

During the process of compiling the systematic review, it was determined that the only research projects that were worthy of consideration were those that achieved success in achieving each and every one of the parameters. This was done in order to guarantee that the review is as comprehensive as it possibly can be. It is possible to gather information about each individual study, such as its title, author, publication date, origin of study location, research study design, and research variables. Some of the information that may be collected includes the following: This information may be provided in a variety of formats, depending on your preference.

Quality Assessment and Data Synthesis

The authors conducted their own independent reviews of a subset of the research listed in the titles and abstracts of the papers to determine which studies could be considered. Following this, the full texts of the studies that meet the inclusion criteria for the systematic review will be read to determine which studies can be used as final inclusions for the purposes of the review. This will be done in order to respond to the question, "Which studies can we use for the review?"

RESULT

Bazyar *et al* (2021) conducted a study with 50 T2DM patients. They showed mean levels of systolic blood pressure (SBP), mean arterial pressure (MAP), pulse pressure (PP), weight, body mass index (BMI), waist and hip circumference (WC, HC), conicity index, and waist-to-height ratio (WHtR) were all lower than they were before the intervention ($p < 0.05$) after 8 weeks of taking melatonin. Also, the median changes in SBP, MAP, PP, weight, BMI, WC, HC, abdominal volume index (AVI), body adiposity index (BAI), lipid accumulation product (LAP), and conicity index were all lower in the intervention group than in the control group ($p < 0.05$). The average levels of a body shape index (ABSI) in the intervention group went up by a lot ($p < 0.001$), which is a good sign. In the intervention group, the median changes in ABSI were much bigger than in the control group ($p < 0.001$).[11]

Table 1. The litelature include in this study

Author	Origin	Method	Sample Size	Result
Bazyar, 2021[11]	Iran	RCT	50	Melatonin supplementation for 8 weeks significantly reduced post-intervention mean levels of SBP, MAP, PP, weight, BMI, WC, HC, BAI, AVI, conicity index, and WHtR ($p < 0.05$). In addition, the intervention group's median changes in SBP, MAP, PP, weight, BMI, WC, HC BAI, AVI, and conicity index were significantly lower than the control group ($p < 0.05$). The mean levels of ABSI in the intervention group increased significantly ($p < 0.001$). The intervention group's median ABSI changes were significantly greater than the control group's ($p < 0.001$).
Kandemir, 2018[12]	Turkey	Clinical trial	40	They examined VEGF-A expression and phosphorylation in all coronary arteries. Staining intensities, biochemical, immunohistochemistry, and transthoracic echocardiography were done. DM decreased p-VEGF-A in group 2 coronary arteries compared to group 1. Melatonin therapy significantly raised VEGF-A constitutive phosphorylation in coronary arteries in group 2 ($p<0.05$). Myocardial enlargement in diabetic rats protected cardiac function ($p<0.05$). VEGF-A phosphorylation by melatonin may protect cardiac muscle fibers and coronary arteries against diabetes mellitus.
Rezvanfar, 2017[13]	Iran	RCT	64	The mean HbA1c (±standard error) after 3 months of melatonin administration was considerably lower than at baseline (7.65% ± 0.086% against 7.1% ± 0.111%, respectively, P = 0.0001). The mean FBG level was considerably lower at the conclusion of the trial (164 ± 5.4 versus 157 ± 5.5, $P < 0.001$). The HDL cholesterol level rose at the conclusion of the research (42 ± 1.3 vs 45 ± 1.39, $P < 0.05$), but there were no significant changes in TG, CHOL, or LDL.

Kandemir *et al* (2018)[12] examined the expression of VEGF-A as well as its phosphorylation in the coronary arteries of all of the groups. Analyses of the staining intensities, biochemistry, immunohistochemistry, and transthoracic echocardiography were carried out. When compared to group 1, diabetes mellitus caused a reduction in the amount of p-VEGF-A in the coronary arteries of group 2. After receiving melatonin administration, the decreased constitutive phosphorylation of VEGF-A that was found in group 2 was also shown to be elevated in coronary arteries ($p < 0.05$). Rats with diabetes exhibited hypertrophy of the myocardium while maintaining normal cardiac function ($p < 0.05$). The phosphorylation of VEGF-A is the mechanism via which the cardio-protective impact of melatonin may mitigate the negative effects of diabetes on the heart muscle fibers and coronary arteries.

Other study by Rezvanfar *et al* (2017)[13] showed the average HbA1c level was much lower than it had been at the beginning of the study therapy with melatonin for three months (7.65% ± 0.086% vs 7.1% ± 0.111%, respectively, P = 0.0001). At the conclusion of the research project, the participants' mean FBG levels were substantially lower than they had been at the beginning (164 ± 5.4 vs 157 ± 5.5, respectively, $P < 0.001$). At the conclusion of the research project, the HDL cholesterol level was found to have increased (42 ± 1.3 vs 45 ± 1.39, respectively, $P < 0.05$), however there were no significant changes noticed in the levels of TG, CHOL, or LDL.

DISCUSSION

Research investigation showed the consumption of melatonin for a period of eight weeks resulted in a substantial reduction in the subjects' post-intervention weight, waist circumference, hip circumference, body mass index, and waist to hip ratio.[11] Melatonin, a broad-spectrum antioxidant, can be utilized to treat a variety of pathologic disorders, owing to its effects on autophagy, endoplasmic reticulum (ER) stress, and oxidative stress.[14] This chemical has the potential to cure neurological illnesses, cancer, cardiovascular disease, and a variety of other clinical issues. It is also important to mention that it regulates sleep problems and reproduction.[15]

Melatonin also has immunomodulatory characteristics due to its capacity to boost cytokine production as well as its anti-apoptotic and antioxidant capabilities.[15] Melatonin has been proposed to influence the immune system via influencing cytokine release from immunocompetent cells. Melatonin influences reproduction by controlling the synthesis of sex hormones in animals that reproduce seasonally. Melatonin reduces estrogen production in long-breeders. Melatonin, on the other hand, stimulates estrogen production in short-breeders throughout the winter. Melatonin's significance in reproduction in humans is unclear.[16]

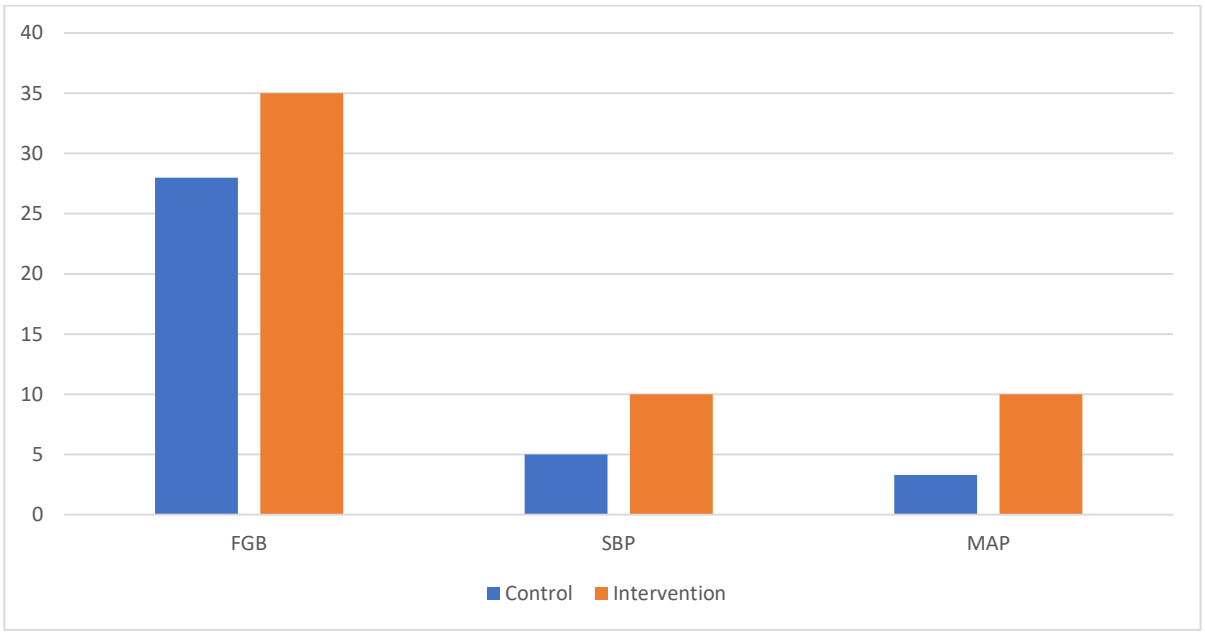

Figure 2. Decreased blood sugar levels and blood pressure

During the dark season, a high melatonin level is connected with a low estrogen synthesis rate. Furthermore, melatonin stimulates steroidogenesis in human granulosa-luteal cells. Melatonin also stimulates progesterone synthesis via its M2 receptors on the corpus luteum. However, several studies have found that melatonin has little effect on granulosa cell estrogen production. Melatonin, when combined with other hormones, influences ovarian function; however, the precise mechanisms of this regulation are unknown.[6,16,17]Melatonin plays a crucial role in the regulation of circadian rhythms, which is required for a balanced metabolism. Melatonin binds to two distinct receptors, referred to as MT1 and MT2, which are respectively encoded by the genes MTRN1A and MTRN1B. When melatonin binds to MT1 and MT2, the subunits and / dissociate, which in turn triggers downstream signaling pathways. These pathways include adenylyl cyclase (AC), phospholipase C (PLC), and phospholipase A2 (PLA2). It has been demonstrated that a disruption in the signaling of melatonin is associated with the development of type 2 diabetes brought on by IR.[18]There is some evidence to suggest that sleep disturbances and irregularities in the circadian clock are contributors to the development of type 2 diabetes and obesity. This lends credence to the hypothesis that the incidence of metabolic illnesses in people who have unconventional lifestyles, such as being exposed to light at night, working night shifts, and eating at unusual hours, is on the rise. As a consequence of this, utilizing both the chronobiotic and cytoprotective qualities of melatonin in conjunction with one another could be an innovative method for treating type 2 diabetes.[18]Melatonin has been found in animal and human research to play a helpful impact in blood glucose management. In pinealectomized mice, the expression of the glucose transporter type 4 (GLUT4) gene is decreased, resulting in glucose intolerance and insulin resistance. Melatonin therapy alleviates these symptoms.[19] Furthermore, melatonin levels in human tooth pulp tissue decrease in type 2 diabetes subjects. Melatonin at pharmaceutical concentrations improved iNOS and SOD activity in hyperglycemic human dental pulp cells (hDPCs), indicating that melatonin has protective effects in human dental pulp tissue under hyperglycemia.[20]

Eight weeks of therapy with insulin (NPH = 1.5 U/100gr/day) and melatonin (0.2 mg/kg/day in drinking water) improves glucose homeostasis and insulin sensitivity of white adipose tissue in rats with streptozotocin (STZ)-induced diabetes.[21] Melatonin synthesis has been shown to decrease in animal models of diabetes, and melatonin therapy (100 mg/kg/day in drinking water for 8 weeks) leads in improved glucose tolerance in high-fat diet-fed mice with insulin resistance. Diabetes also decreases testosterone production.[22]Melatonin (10 mcg/kg/day in drinking water) has been demonstrated to alleviate the negative effects of diabetes on testosterone production in rats by enhancing glucose metabolism in the Leydig cells and stimulating acetate formation, a precursor for cholesterol synthesis. Patients with T2DM produce less melatonin at night than those who do not have diabetes. Several studies have found that a single dosage of melatonin (1 mg and 5 mg, respectively) affects the glucose tolerance test in the morning and evening in healthy postmenopausal and premenopausal women. Chronic therapy with prolonged-release melatonin (2 mg) over a 5-month period, on the other hand, lowers HbA1c and improves glycemic control.[23] Furthermore, 3 months of melatonin (6 mg) therapy resulted in improved glycemic control in T2DM patients. Melatonin (10 mg) and zinc acetate (50 mg) added to metformin resulted in a better tissue response than metformin alone in patients with poorly managed T2DM. Melatonin (3 mg/day) treatment for 12 weeks enhanced insulin sensitivity as well as inflammatory state in obese patients with Acanthosis Nigricans.[13]

Melatonin's anti-oxidative action efficiently reduces oxidative stress, which plays an essential role in the development of many complications of illnesses such as diabetes. Furthermore, by neutralizing reactive oxygen species, this hormone protects pancreatic beta cells, which have a poor antioxidant capacity. According to a recent comprehensive study, melatonin may have a role in improving glycemic management by enhancing insulin sensitivity and decreasing fasting glucose.[24]

Studies in the laboratory have shown that melatonin may have a positive impact on how the body processes glucose. While administration of melatonin to insulin-resistant mice reversed insulin resistance and improved glucose metabolism, oral consumption of melatonin protected rats predisposed to diabetes from developing hyperlipidemia, hyperglycemia, and hyperleptinemia while receiving a high-calorie diet.6 On the other hand, oral consumption of melatonin protected rats predisposed to diabetes from developing hyperleptinemia.[25]

Melatonin increased the glucose sensitivity of human pancreatic islet cells when they were exposed to it for a longer period of time, as shown by in vitro investigations using human islet cells. Melatonin exposure activates the phosphatidylinositol-3-kinase/protein kinase B survival pathway and the mitogen-activated protein kinase/extracellular signal-regulated kinase growth pathway of in vitro islet cells. This could potentially explain the low density of pancreatic islet cells that was observed in rats following pinealectomy.[25]

CONCLUSION

According to the findings of this paper, patients who used melatonin supplements reported higher decreases in their blood sugar levels. However, this trend was not constant when looking at blood pressure and other indicators.

REFERENCE

[1]. Association AD. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2014;37(Supplement_1):S81–90.

[2]. International Diabetes Federation. Diabetes. Brussels: IDF; 2017.

[3]. Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. Diabetes Res Clin Pract. 2010;87(1):4–14.

[4]. Du W, Peng S-M, Liu Z, Shi L, Tan L-F, Zou X-Q. Hypoglycemic effect of the water extract of Pu-erh tea. J Agric Food Chem. 2012;60(40):10126–32.

[5]. Sivertsen B, Lallukka T, Petrie KJ, Steingrímsdóttir ÓA, Stubhaug A, Nielsen CS. Sleep and pain sensitivity in adults. Pain. Agustus 2015;156(8):1433–9.

[6]. Szewczyk PB, Dziuba AM, Poniewierka E. Melatonin–metabolism and the role of pineal hormone. Pielęgniarstwo i Zdr Publiczne Nurs Public Heal. 2018;8(2):135–9.

[7]. Frese T, Bach AG, Mühlbauer E, Pönicke K, Brömme H-J, Welp A, et al. Pineal melatonin synthesis is decreased in type 2 diabetic Goto–Kakizaki rats. Life Sci. 2009;85(13–14):526–33.

[8]. Ozkanlar S, Kara A, Sengul E, Simsek N, Karadeniz A, Kurt N. Melatonin modulates the immune system response and inflammation in diabetic rats experimentally-induced by alloxan. Horm Metab Res. 2016;48(02):137–44.

[9]. Ríos-Lugo MJ, Cano P, Jiménez-Ortega V, Fernández-Mateos MP, Scacchi PA, Cardinali DP, et al. Melatonin effect on plasma adiponectin, leptin, insulin, glucose, triglycerides and cholesterol in normal and high fat–fed rats. J Pineal Res. 2010;49(4):342–8.

[10]. Pevet P, Challet E. Melatonin: both master clock output and internal time-giver in the circadian clocks network. J Physiol. 2011;105(4–6):170–82.

[11]. Bazyar H, Zare Javid A, Bavi Behbahani H, Moradi F, Moradi Poode B, Amiri P. Consumption of melatonin supplement improves cardiovascular disease risk factors and anthropometric indices in type 2 diabetes mellitus patients: a double-blind, randomized, placebo-controlled trial. Trials. Maret 2021;22(1):231.

[12]. Kandemir YB, Tosun V, Korucuk N, Bozdemir MN. Melatonin protects against streptozotocin-induced diabetic cardiomyopathy by the phosphorylation of vascular endothelial growth factor-A (VEGF-A). Cell Mol Biol. 2018;64(14):47–52.

[13]. Rezvanfar MR, Heshmati G, Chehrei A, Haghverdi F, Rafiee F, Rezvanfar F. Effect of bedtime melatonin consumption on diabetes control and lipid profile. Int J Diabetes Dev Ctries. 2017;37(1):74–7.

[14]. Boga JA, Caballero B, Potes Y, Perez-Martinez Z, Reiter RJ, Vega-Naredo I, et al. Therapeutic potential of melatonin related to its role as an autophagy regulator: A review. J Pineal Res. 2019;66(1):e12534.

[15]. She Q, Han Z, Liang S, Xu W, Li X, Zhao Y, et al. Impacts of circadian rhythm and melatonin on the specific activities of immune and antioxidant enzymes of the Chinese mitten crab (Eriocheir sinensis). Fish Shellfish Immunol. 2019;89:345–53.

[16]. Pourhanifeh MH, Hosseinzadeh A, Dehdashtian E, Hemati K, Mehrzadi S. Melatonin: new insights on its therapeutic properties in diabetic complications. Diabetol Metab Syndr [Internet]. 2020;12(1):30. Tersedia pada: https://doi.org/10.1186/s13098-020-00537-z

[17]. Zhang C, Zhang Q, Pang Y, Song X, Zhou N, Wang J, et al. The protective effects of melatonin on oxidative damage and the immune system of the Chinese mitten crab (Eriocheir sinensis) exposed to deltamethrin. Sci Total Environ. 2019;653:1426–34.

[18]. Jockers R, Delagrange P, Dubocovich ML, Markus RP, Renault N, Tosini G, et al. Update on melatonin receptors: IUPHAR Review 20. Br J Pharmacol. 2016;173(18):2702–25.

[19]. Rodrigues SC, Pantaleão L, Lellis-Santos C, Veras K, Amaral F, Anhê G, et al. Increased corticosterone levels contribute to glucose intolerance induced by the absence of melatonin. Wiley Online Library; 2013.

[20]. Sun H, Wang X, Chen J, Gusdon AM, Song K, Li L, et al. Melatonin Treatment Improves Insulin Resistance and Pigmentation in Obese Patients with Acanthosis Nigricans. Int J Endocrinol. 2018;2018:2304746.

[21]. de Oliveira AC, Andreotti S, Sertie RAL, Campana AB, de Proença ARG, Vasconcelos RP, et al. Combined treatment with melatonin and insulin improves glycemic control, white adipose tissue metabolism and reproductive axis of diabetic male rats. Life Sci. 2018;199:158–66.

[22]. Sartori C, Dessen P, Mathieu C, Monney A, Bloch J, Nicod P, et al. Melatonin improves glucose homeostasis and endothelial vascular function in high-fat diet-fed insulin-resistant mice. Endocrinology. 2009;150(12):5311–7.
[23]. Garfinkel D, Zorin M, Wainstein J, Matas Z, Laudon M, Zisapel N. Efficacy and safety of prolonged-release melatonin in insomnia patients with diabetes: a randomized, double-blind, crossover study. Diabetes, Metab Syndr Obes targets Ther. 2011;4:307.
[24]. Doosti-Irani A, Ostadmohammadi V, Mirhosseini N, Mansournia MA, Reiter RJ, Kashanian M, et al. The effects of melatonin supplementation on glycemic control: a systematic review and meta-analysis of randomized controlled trials. Horm Metab Res. 2018;50(11):783–90.
[25]. McMullan CJ, Schernhammer ES, Rimm EB, Hu FB, Forman JP. Melatonin Secretion and the Incidence of Type 2Diabetes.JAMA[Internet].3 April 2013;309(13):1388–96. Tersedia pada: https://doi.org/10.1001/jama.2013.2710