Melatonin as an alternative in the treatment of diabetes mellitus and its complications: A literature review

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Gabriela Feres de Marchi[1] and Patrícia Gelli Feres de Marchi [2]

ABSTRACT

Diabetes Mellitus (DM) is a complex metabolic disorder with multifactorial causes caused by resistance to the action of insulin, or the secretion of this hormone, or both. The disease can be divided into type 1 or 2 diabetes mellitus and gestational diabetes. Among its complications we find vision problems, kidney problems, stroke, stroke, heart attack, diabetic coma and foot ulcers or amputations. The prevalence of the pathology has increased worldwide in recent years, including in Brazil, linked to causes such as lifestyle and socioeconomic indicators, becoming a public health problem. Melatonin is a promising hormone in the treatment of various medical conditions due to its relationship with several functions in the body because it is responsible for organizing the circadian cycle, among these functions, the regulation of glucose, production and secretion of insulin by pancreatic beta cells. This review study searched the main databases for evidence of the application of exogenous melatonin to control DM or its complications. Since its first exogenous use described in 1960, the effects of melatonin use have been studied and recently applied in humans, in vitro and in animals as a possibility of treatment for DM in its most varied types. We conclude that the use of melatonin as an alternative to treatment, although very promising, should still be better studied in humans, in order to adjust doses, routes and times of application.

Keywords: Blood glucose, Insulin, Obesity, Alternative treatment.

[1] Undergraduate student in Bachelor of Nursing at the Federal University of Mato Grosso (UFMT – Araguaia Campus), MT

[2] Doctor., Professor, Federal University of Mato Grosso (UFMT – Araguaia Campus), MT

INTRODUCTION

Diabetes Mellitus is a complex metabolic disorder characterized by high concentrations of glucose in the blood, as well as resistance to insulin action, insufficient insulin secretion, or both. Among the causes for the onset of the disease are genetic disorders, diseases that cause damage to the pancreas, excess growth hormone and glucocorticoids, medications, chemicals or infections. The disease can be characterized as type 1 (DM1), when there is a deficiency in the function of pancreatic beta cells, which are responsible for synthesizing and secreting insulin. Type 2 diabetes (T2DM) is characterized by insulin resistance and a relative deficiency of insulin secretion, when the plasma concentration of insulin becomes insufficient to maintain normal blood glucose homeostasis. Finally, gestational diabetes mellitus (GDM) occurs when there is a glucose intolerance first identified during the gestational period, which usually happens in the third trimester of pregnancy in most women and is related to a higher likelihood of developing T2DM in the future (Solis-Herrera et al., 2018). Inadequate control of glycemic indexes in the body can lead to complications for the individual that affect their quality of life, such as vision problems, kidney problems, stroke, stroke, heart attack, foot ulcers or amputations, and diabetic coma, such complications can lead to death (Neves et al., 2023). According to the WHO, in 2019 diabetes was the direct cause of 1.5 million deaths worldwide, in addition to 460,000 deaths from complications such as diabetic nephropathy and hyperglycemia. The WHO also states that both the number of cases and the prevalence of the disease have steadily increased in countries in recent decades, including Brazil (WHO, 2019)

In Brazil, according to the Brazilian Diabetes Society, there were 15.8 million people with diabetes mellitus in 2021, with a mortality rate of 30.2 individuals per 100 thousand inhabitants in 2019 (Pititto et al., 2023). Social indicators such as low schooling, low income, age, and race are associated with diabetes cases, increased incidence, and higher occurrence of complications, concomitantly there has been an increase in the use of medication and medical care by the Brazilian population in recent years (Malta et al., 2022, Peres et al., 2023, Neves et al., 2023). Even with the increase in the use of medications, adherence to drug treatment for diabetes is still considered low, with an average of 78.3% adherence (Faria, 2013). In this scenario, new drugs with fewer side effects are being tested in order to increase treatment adherence, among them, melatonin has been the target of research.

Melatonin is a hormone produced mainly by the pineal gland at night during the day, its main function is to transmit information about the light cycle during the day/night. This information organizes seasonal rhythmicity functions in the body, in addition, melatonin can also be used in the organization of circadian rhythms, stabilizing and strengthening their coupling. Other physiological functions may depend on such circadian organization, such as immune defenses, antioxidants, hemostasis, and glucose regulation (Claustrat and Chazot, 2005). Due to its action in several

functions of the body and its short half-life (Maganhin et al., 2008), the administration of exogenous melatonin has become a therapeutic option.

The first exogenous administration of melatonin, isolated for the first time in the 1950s, was described in 1960 with the administration of 200 mg intravenously, obtaining a mild sedative effect (Dawson, 1993). More recent studies prove the safety and efficacy of the administration of exogenous melatonin with various therapeutic objectives, such as regulation of the circadian cycle, reduction of inflammatory activity and action in the modulation of the immune, cardiovascular and gastrointestinal systems, in addition to acting in synergism with other drugs in the mitigation of infectious processes (Junior et al., 2019)

METHODOLOGY

For this study, the bibliographic research method was used with the words "melatonin" and "diabetes" in the scientific databases Google Scholar, LILACS, Scielo, PubMed and CAPES Journals. Articles and theses in Portuguese, English and Spanish will be selected from 2018 to 2024. Documents that did not match the research theme or that did not fit into the selected period were excluded.

DISCUSSION

Moreira (2022) relates circadian rhythm disturbance to deficient melatonin synthesis and how the suppression of this hormone becomes a risk factor for the development of DM2. This study shows the physiological mechanisms of melatonin and insulin production and secretion in the human body and highlights that pancreatic beta cells, responsible for insulin production, have melatonin receptors (MT1 and MT2) that can, in different ways, alter insulin secretion and generate insulin resistance in the body (Moreira et al., 2022). The following year, Ferreira (2023) evidences the direct relationship between melatonin and insulin production, bringing a study of pinealectomized rats that, upon receiving melatonin, obtained an increase in insulin production in pancreatic beta cells and expansion of insulin receptors in hepatocyte membranes. The two studies evaluate the therapeutic potential of melatonin in DM and instigate further research on the subject, but have not yet analyzed its in vivo application (Ferreira, 2023)

Awni found, through quantification of blood samples collected from 46 diabetic and non-diabetic patients, the abnormal production of oxidative stress markers, nitric oxide and melatonin can contribute to the pathogenesis of DM2. This work focused on the negative potential of melatonin in its relationship with the pathology studied (Awni, 2022).

Martorina (2023) was the first crossover, double-blind, placebo-controlled, randomized study to evaluate the role of melatonin in the glycemic variability of patients with DM2, this study shows

that the use of melatonin in a dose of 3mg taken at 21:00 increases glycemic variability compared to placebo, a result opposite to that expected that can be explained by the residual diurnal effects, proximal prospective effects, impairment of the distal prospective effect of melatonin caused by exogenous melatonin, and genetic characteristics of patients. The study also notes that lower doses, with lower risks of residual effects in the morning, may show different results in the patient's glycemic variability (Martorina, 2023). Analogous to this study, Sousa (2024) had supplemented a group of overweight night shift nursing workers with the same dose of 3mg, with the aim of evaluating the effects of melatonin supplementation on diabetes risk markers, according to the lipid profile of the diet. As a result, Souza found that hormone supplementation for 12 weeks did not affect DM2 risk markers according to the dietary fat profile and also did not modify the fat consumption profile over the same period (Sousa, 2024).

However, when evaluating the action of melatonin on mononuclear (NM) cells and the placenta of diabetic mothers, Louis (2018) concludes that melatonin was able to reduce oxidative stress and apoptosis rates in MN cells in the maternal blood of diabetic mothers and was able to act on placental tissue cells by increasing apoptosis rates in the villous layer of the placenta of hyperglycemic mothers, suggesting that this hormone may act in the process of maintenance and development of the fetus in pregnancies of diabetic mothers (Louis, 2018). And aimed at the treatment of diabetic wounds, a possible complication of DM, the use of exogenous melatonin showed excellent results, promoting wound healing and suppressing the inflammatory response, results obtained in the study with in vitro and in vivo models (Liu, 2020). When associated with bacterial cellulose-based dressings, melatonin supplementation is associated with increased fibroblast production, synthesis and deposition of collagen fibers, as well as decreased inflammatory effects (Oliveira et al., 2023)

More broadly, melatonin is also associated with several other applications, such as reducing oxidative stress and restoring the viscosity of cervical mucus in women with HPV (Human Papillomavirus) (Cotrim et al., 2020), immunomodulatory effects on human colostrum polymorphonuclear cells, which in turn may play a crucial role in tumor resolution with MCF-7 cells through its mediation and inflammatory action (Sousa et al., 2022), when associated with leptin and adiponectin, the hormone melatonin can restore the proliferation of CD4+ T lymphocytes in obese mothers to the levels found in more eutrophic mothers (Pereira et al., 2023), a relationship between melatonin supplementation and lipid indices with the reduction of total cholesterol and triglycerides was also identified (Halpern, 2019).

In studies with rodents, it was observed from the treatment with melatonin a decrease in morphometric, glycemic, inflammatory parameters associated with diabetes, in addition to the regulation of the balance of oxidative stress through the increase in the expression of antioxidant

enzymes, generating regulation of total testosterone and androgen receptor levels (Alves, 2020), when associated with insulin administration, can have a protective effect, by inhibiting or reducing the destruction of pancreatic β cells and maintaining insulin levels close to the control group (Melo, 2020), the protective effect on steatosis in the liver of female rats with GDM is also evidenced (Santos, 2020), shorter time of contraction of skin wounds in Wistar rats with diabetes treated with a topical formulation containing melatonin (Souza, 2022) and potentiation of the action of metformin as a maintenance treatment, bringing better quality of life (Silva, 2018), the attenuation of the effects of a high-fat diet was also observed, suggesting a potential in the use of melatonin as a prevention of obesity in individuals with difficulty in adhering to diet programs (Farias, 2019).

CONCLUSION

Physiologically, the hormone melatonin is present in the regulation of several functions of the body, including the production and secretion of insulin, and can be negative or positive, but there is a promising possibility in the treatment of obesity, DM and its complications, and the therapeutic dose for humans, as well as the best period and best route of application, should still be defined by new studies.

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