ASSESSMENT OF IMMUNOLOGICAL EFFECTS OF MELATONIN IN IMMUNODEFICIENT POPULATION: A SYSTEMATIC REVIEW OF RANDOMIZED CONTROLLED TRIALS

Hodnotenie imunologických účinkov melatonínu na imunodeficientnú populáciu: systematický prehľad náhodne kontrolovaných pokusov

Tetiana I. Liadova[1], Mykola M. Popov[1], Diana M. Dorosh,[1] Alexander V. Martynenko[2], Olga V. Volobueva[1], Iryna V. Kadyhrob,[3] Olga G. Sorokina[1], Alla P. Gamilovskaya[1], Olesya V. Gololobova[1], Natalia V. Shepylieva[1]

[1.] V. N. Karazin Kharkiv National University, School of Medicine, Department of General and Clinical Immunology and Allergology, head: Tetiana I. Liadova Doctor of Medicine, Professor.
[2.] V. N. Karazin Kharkiv National University, School of Medicine, Department of Hygiene and Social Medicine, head: Zhanna V. Sotnikova-Meleshkina, Ph.D., Assistant Professor.
[3.] Municipal non-profit enterprise «State Dermatovenerology Dispansary №1» of Kharkiv municipal council, head: Iryna V. Kadyhrob, Ph.D., Assistant Professor.

SUMMARY

The study and usage of melatonin in various fields of medicine has become relevant in recent years. Many studies show high efficacy of melatonin treatment in different diseases that are accompanied by immunodeficiency in humans: oncology, viral and infectious diseases, neuro-degenerative diseases, heart disease, kidney disease, and liver disease. However, the separately immunomodulatory effects of melatonin in diseases accompanied by such conditions has not been studied. We conducted a qualitative systematic review of randomized controlled trials (RCTs) using the recommended guidelines of the Cochrane Handbook for Systematic Reviews of Interventions and PRISMA regarding the disclosure of status and changes in the immune system during melatonin treatment in adult patients in order to investigate immunomodulatory effect in diseases accompanied by immunodeficiency. We searched in 6 electronic databases from the moment they were created until May 2020. All trials investigated diseases accompanied by immunodeficiency conditions using melatonin as monotherapy and as adjunctive treatment and included analysis of specific indicators: TNF-α, IL-1β, IL-1Ra, IL-2, IL-6, IL-12, IL-8, IL- 4, IL-10, CD44, CD133, YKL-40. These criteria were used to guide our test quality assessment. We included 9 RCTs published between 1964 and 2020, and included 365 patients. The ten authors of the review independently checked the search results, extracted data and evaluated the quality of the research. We estimated statistical heterogeneity using IBM SPSS Statistics. The risk of bias of each included study was assessed using the web 'riskofbias.info' tool. The quality of the evidence was assessed using GLMM methods. We found that melatonin substantially improved the status of the immune system (heterogeneity $P < 0.05$). The effects were consistent between melatonin dose, duration of treatment and baseline immune status. No serious adverse events were reported.

Significant immunomodulatory effect, low side effects and low costs associated with this intervention indicate the great potential of melatonin in the treatment of diseases accompanied by immunodeficiency. Confirmation of immunomodulatory effect and safety of melatonin in diseases associated with such conditions should require blind, independent RCT.

Keywords: Immunity, cytokines, immunodeficiency, immunostimulatory therapy, melatonin.

SÚHRN

Skúmanie a použitie melatonínu v rôznych oblastiach medicíny začalo byť aktuálne v posledných rokoch. Veľa štúdií ukazuje vysokú efektívnosť liečby melatonínom pri rôznych ochoreniach sprevádzaných imunodeficitom človeka (onkologické ochorenia, vírusové a infekčné ochorenia, neurodegeneratívne ochorenia, ochorenia srdca, obličiek aj pečene). Napriek tomu imunomodulačný efekt melatonínu pri týchto ochoreniach nebol skúmaný. Vykonali sme systematický prehľad randomizovaných kontrolovaných štúdií (RCT), s použitím odporúčaných postupov Cochranovej príručky a postupov PRISMA, ktoré sa týkajú zmien imunitného systému pri liečbe melatonínom u dospelých pacientov s ochoreniami sprevádzanými imunodeficitom. Prezreli sme 6 elektronických databáz od i vzniku do mája roku 2020. Všetky štúdie skúmali ochorenia sprevádzané imunodeficienciou, kde sa melatonín používal ako monoterapia a pomocná liečba, a obsahovali analýzu jednotlivých ukazovateľov: TNF-α, IL-1β, IL-1Ra, IL-2, IL-6, IL-12, IL-8, IL- 4, IL-10, CD44, CD133, YKL-40. Tieto kritériá boli zohľadnené v našom hodnotení kvality testu. Začlenili sme 9 RCT, zverejnených v priebehu rokov 1964 až 2020 a 365 pacientov. Desať autorov prehľadu nezávisle preverovalo výsledky vyhľadávania, sťahovali údaje a hodnotili kvalitu výskumu. Hodnotili sme štatistickú nerovnorodosť používajúc štatistiku IBM SPSS Statistics. Riziko odchýlky každej zapojenej štúdie bolo hodnotené prostredníctvom web-nástroja „riskofbias.info“. Kvalita dôkazov bola hodnotená pomocou metódy GLMM. Zistili sme, že melatonín výrazne vylepšil stav imunitného systému (heterogénnosť $P < 0.05$). Účinky súviseli s dávkou melatonínu, trvaním liečby a základným imunitným stavom. Neboli hlásené žiadne závažné nežiaduce účinky. Výrazný imunomodulačný účinok, nepatrné vedľajšie účinky a nízke náklady svedčia o veľkom potenciáli melatonínu pri liečbe ochorení sprevádzaných imunodeficitom. Potvrdenie imunomodulačného účinku a bezpečnosti melatonínu pri ochoreniach súvisiacich s takými stavmi si bude vyžadovať ďalšie štúdium (nezávislú RCT).

Kľúčové slová: imunita, cytokíny, imunodeficiencia, imunostimulačná terapia, melatonín.

INTRODUCTION

Description of the condition

A huge percentage of the population is affected by immunodeficiency. Secondary immunocompromised conditions can result from HIV infection, malnutrition, post-traumatic stress

disorder, aging and immunosenescence, radiation therapy, particular medications (e.g., immunosuppressive drugs after graft transplantation, disease-modifying anti-rheumatic drugs, chemotherapy in malignancies, prolonged corticosteroid therapy, etc.), many types of cancer (leukemias, lymphomas, etc.), protein-losing enteropathy, burns, uremia, loss of lymphoid organs (e.g., splenectomy, appendectomy, resection of the small intestine containing Peyer's patches, etc.), and some autoimmune diseases and other disorders [1]. The presence of immunodeficiency significantly affects the efficacy of basic therapy and prognosis of disease. People living with HIV, even after suppressive antiretroviral therapy (ART), experience high incidence of non-AIDS associated comorbidities, including cardiovascular disease (CVD), frailty, and osteoporosis, liver and kidney disease, and non-AIDS-associated cancers [2]. Chronic immune activation and inflammation have been identified as the main factors that cause comorbidities and adversely affect their treatment. [3,4,5]. A dominant approach to treatment for secondary immunocompromised conditions is immune enhancement therapy [1]. There is a variety of immunotherapy methods, among which the main ones are immunoglobulin therapy [6,1], use of transfer factor [7], use of interferon gamma [8], use of cytokines in the immunotherapy of advanced malignancies [9], use of nutritional supplements (Vitamins A, C, E and B6, Iron, Zinc, Selenium, and Copper etc.) [8]. But their usage can be severely limited by undesirable side effects, contraindications, selective and partial action. Therefore, the search and the study of drugs increasing immunity is still relevant.

Description of the interventions

The study of melatonin as a prospective substance has been actively conducted for many years in various fields of medicine. This interest is due to its unique features associated with antioxidant and anti-inflammatory properties. At first, melatonin (MLT; N-acetyl-5-methoxy-tryptamine) was thought to be of purely pineal gland origin, but recent studies have shown that MLT synthesis occurs in many organs and systems, so obviously it has many functions. Thus, MLT is a molecule that regulates circadian day–night rhythms and seasonal biorhythms [10,11]. Besides studies have revealed that skin in mammals possesses a fully functioning melatoninergic system [12,13]. The concentration of MLT in the skin is several times higher than that in plasma [14]. In addition, the studies have discovered that serum MLT levels increase dramatically during pregnancy, so that levels increase hundredfold in the third trimester compared to healthy non-pregnant women. Studies report that MLT is involved in the hematopoietic system [15]. Researchers report that MLT is involved in the hematopoietic system. In particular, thrombopoiesis has been proven to be stimulated by MLT [16]. Furthermore, MLT plays a key role in the immune system, and MLT receptors are expressed on the membrane of immune cells [17]. There are many studies that report the efficacy of MLT treatment in cancer and its oncostatic properties [18,19,20,21,22]. In addition to its direct antitumor activity, the effects of modulation in cancer chemotherapy have already been proved by enhancing its therapeutic efficacy and reducing its toxicity [23]. Adjuvant melatonin delayed the onset of oral mucositis, which enables uninterrupted cancer treatment [24] and minimizes the adverse effects of radiotherapy on blood cell count reductions

by attenuating the adverse influence of radiation [25,26]. Melatonin administration reduces oxidative stress and improves dyspnea in chronic obstructive pulmonary disease (COPD) [27]. The effect of MLT in patients with herpes infection as an alternative to acyclovir therapy has also been studied. Researches have shown that the melatonin is more effective compared to acyclovir [28].

Thus, many studies have shown therapeutic efficacy in conditions that are accompanied by immunosuppression using MLT as a combination, mono and adjuvant treatment. Recent discoveries confirm the need in further in-depth study of MLT.

The task of our systematic review is to evaluate the immunomodulatory effect of melatonin in diseases accompanied by immunodeficiency states.

How the intervention might work

Neuroendocrine system has been reported to modulate immune response through neuropeptides and neurohormones. There is data which indicates the existence of a neuro-endocrine-immune system regulatory axis. At the same time, there is growing evidence that the pineal gland has anti-neoplastic properties, which include the effect of its principal hormone, MLT, on the immune system through the release of cytokines by activated T-cells and monocytes [29]. MLT has been demonstrated to modulate immune function in cancer patients by activating the cytokine system which exerts growth-inhibitory properties over a wide range of tumor cell types. Furthermore, MLT plays a critical role in host defence against the progression of neoplasia by stimulating the cytotoxic activity of macrophages and monocytes [29]. When macrophages are exposed to inflammatory stimuli, they secrete cytokines such as tumor necrosis factor (TNF), IL-1, IL-6, IL-8, and IL-12 [30]. The inflammatory response is beneficial for the host when the aforementioned cytokines are produced in appropriate amounts, but toxic when produced in a deregulated fashion. For example, excessive production of IL-1β and TNF triggers an acute generalized inflammatory response characteristic of septic shock and multi-organ failure [31]. Therefore, the correlation of TNF and interleukins before and after MLT intervention clearly reflects the efficacy of its immunomodulatory effects in immunodeficient population.

Why it is important to do this overview

The most common causes of clinical immunodeficiency are secondary to other diseases, or their treatment, and can be either humoral or cellular in type [32]. Humoral causes include loss of antibodies in the renal tract, e. g. nephrotic syndrome, and decreased synthesis of antibodies - in lymphoid malignancy, in cytotoxic and steroid therapy and in severe protein - calorie malnutrition. Cellular causes include viral infections, especially human immunodeficiency virus (HIV), but also Epstein-Barr virus (EBV), cytomegalovirus (CMV) and others, lymphoid malignancy, advanced non-lymphoid malignancy, steroid and cytotoxic therapy and severe protein-calorie malnutrition [1,32]. Thus, conditions accompanied by immunodeficiency account for a significant proportion of the human population, which justifies the great relevance and attention in modern medicine. As is commonly

known, no systematic review is available that addresses the evaluation of immunological effects and efficacy of MLT in immunodeficient population. Most of the existing systematic reviews provide a detailed description of each case with different nosologies. Therefore, we need a systematic review to analyze general immunological effects of MLT in various diseases that can provide confirmation of the possibility of using it as an alternative immunomodulator.

Objectives

Investigate and analyze the immunomodulatory effect of melatonin in diseases accompanied by immunodeficiency states and confirm the possibility of its use as an alternative immunomodulator.

METHODS

NOTE: this update uses individual studies, not reviews, for the basis of all analyses.

A systematic review of the literature concerning the disclosure of status and changes in the immune system during melatonin treatment in adult patients to investigate immunomodulatory in diseases accompanied by immunodeficiency was carried out using the recommended guidelines provided by the Cochrane Handbook for Systematic Reviews of Interventions [33] and the PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses of Studies That Evaluate Health Care Interventions [34, 35].

Types of studies

We included Randomized controlled trials (RCTs) for MLT in people with immunodeficiency, in any dose, if they reported clinically relevant outcomes (listed in the section below).

Types of participants

We included adult patients of different ages with the following diseases: cancer, viral and infectious diseases (HIV, herpesvirus diseases associated with types HHV-1, HHV-2, VZV, HHV-6; infectious myocarditis, pyelonephritis, hepatitis and sepsis), radiation sickness accompanied by immunodeficiency.

Types of interventions

We considered the use of melatonin both as monotherapy and as adjunctive treatment without dose restrictions compared to placebo. We included randomized controlled trials (RCTs) that evaluated the efficacy of the therapy and excluded studies in which interventions were not compared with the placebo group [36,37]. We report the findings of all interventions in the results and findings of the review.

Types of outcome measures

We classified the conditions accompanied by immunodeficiencies and their dynamics according to the following indicators: TNF-α, IL-1β, IL-1Ra, IL-2, IL-6, IL-12, IL-8, IL- 4, IL-10, CD44, CD133, YKL-40.

Search Methods for Identification of Studies

We performed a literature search during April and May 2020 using MEDLINE (1950 – May 2020), EMBASE (1980 – May 2020), Cochrane Central Register of Controlled Trials (the Cochrane Library (2016 – May 2020), PubMed (1996 – May 2020), U.S. National Library of Medicine ClinicalTrials.gov (1997 – May 2020), ResearchGate (2008 – May 2020), Keywords included "cancer", "HIV", "septicemia", "HHV-1", "HHV-2", "VZV", "multiple sclerosis", "chronic kidney disease", "melanoma" and were combined with "melatonin". The search was restricted to the English language and an adult study population. Included study designs comprised only randomized controlled trials (RCTs). We included adult patients of different ages with the following diseases: cancer, viral and infectious diseases (HIV, herpesvirus diseases associated with types HHV-1, HHV-2, VZV, HHV-6; infectious myocarditis, pyelonephritis, hepatitis and sepsis), multiple sclerosis accompanied by immunodeficiency conditions.

Study Selection Criteria

Two teams of two abstractors each (TL/DD; MP/OV) independently assessed titles, abstracts, and/or the full text paper of the records retrieved from the electronic databases and hand searched for possible inclusion according to the predefined selection criteria, i.e., any randomized controlled trial evaluating the effects of melatonin as an immunomodulator in which validated measurement tools were used for evaluation, using a predefined data extraction form created as a Microsoft Excel® spreadsheet (designed by DD). Studies published in the non-English language were excluded. Disagreements between the authors were resolved by the senior author (MP).

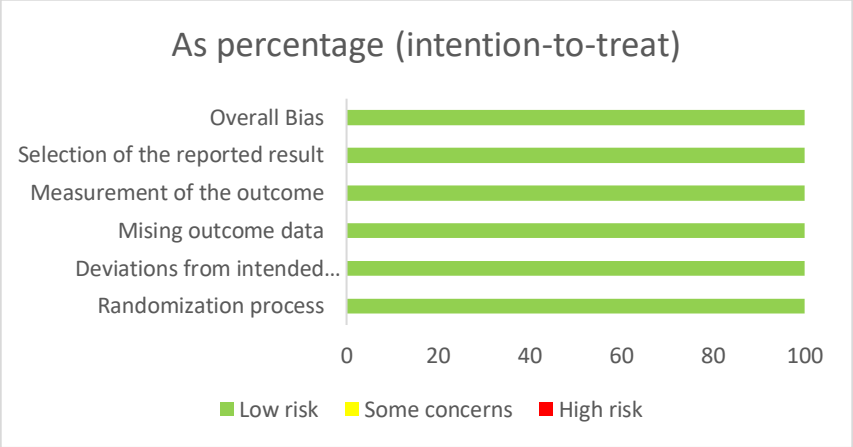
Assessment of Methodology Quality

The data were extracted by two teams TL/DD; MP/OV individually and were validated by MP by double data entry. Two abstractors independently evaluated the risk of bias (OM/DD) of the included studies. And three abstractors independently evaluated the overall quality of the evidence (OG/IK/OS).

Risk of bias in included trials

Two abstractors (OM/DD) independently assessed the risk of bias for each included trial using web 'riskofbias.info' tool (Fig. 1.). We resolved any conflicts in the assessment of methodological quality of eligible studies through discussion, and if necessary, through evaluation by the senior author (MP).

Figure 1. Risk of bias.



Data Extraction and Analysis

The data was extracted by two teams of two abstractors (TL/DD; MP/OV) individually and validated by MP, by double data entry. Details of study population, interventions, and outcomes were extracted using a standardized data extraction form, which included general information, trial characteristics, study population characteristic, interventions, and outcomes (Fig. 2). The primary outcomes of the review included the level of such indicators: TNF-α, IL-1β, IL-1Ra, IL-2, IL-6, IL-12, IL-8, IL- 4, IL-10, CD44, CD133, YKL-40 and different doses of melatonin.

This study is a "qualitative systematic review" without meta-analysis. We summarize and present the results in several tables. To identify the significant findings in each paper, we considered a *P* value < 0.05 as a level of statistical significance. There were several reasons that made us decide not to carry out a meta-analysis in this review. First, there were obvious clinical inconsistencies among the papers in terms of the study population, time of outcomes assessment, and the dosing of melatonin. Second, the data was presented in a format of median and range in the papers. Also, presenting the results in median and range by the papers could indicate that the respective data was not normally distributed, and therefore the normality assumption could not be achieved to conduct a valid meta-analysis. Finally, in many papers the data was only presented in a figure or graph, and tabular data was not available. We contacted the authors to obtain tabular data; and the authors of the two works did not provide us with the necessary information [45,46].

PRISMA 2009 Flow Diagram

Our strategy of searching for the subject of immunological effects of melatonin in the immunodeficiency population has yielded 875 results (Fig. 2). There have been obtained nine studies to meet our inclusion criteria (n=365 patients), that is why the total number is 9 studies [38-46] included in the present review (Table 1). The studies included the use of melatonin both as a monotherapy and as an adjunctive therapy with a native dosage that was comparable to placebo. The treatment duration differed basically in all the studies (Table 1). The results of the randomized controlled trials were based

on various indicators, mainly TNF-α and IL-6 levels (Alamili 2014, Alamdari 2014, Hernández-Velázquez 2016, Zhao 2018, Bazyar 2019) and to a lesser extent IL-1β, IL-1Ra, IL-8, IL-10 (Cavalcante 2012, Alamili 2014, Sánchez-López 2018, Yosefifard 2019) (Table 2).

Fig. 2. Flow chart of the literature search, screening, and inclusion of the studies

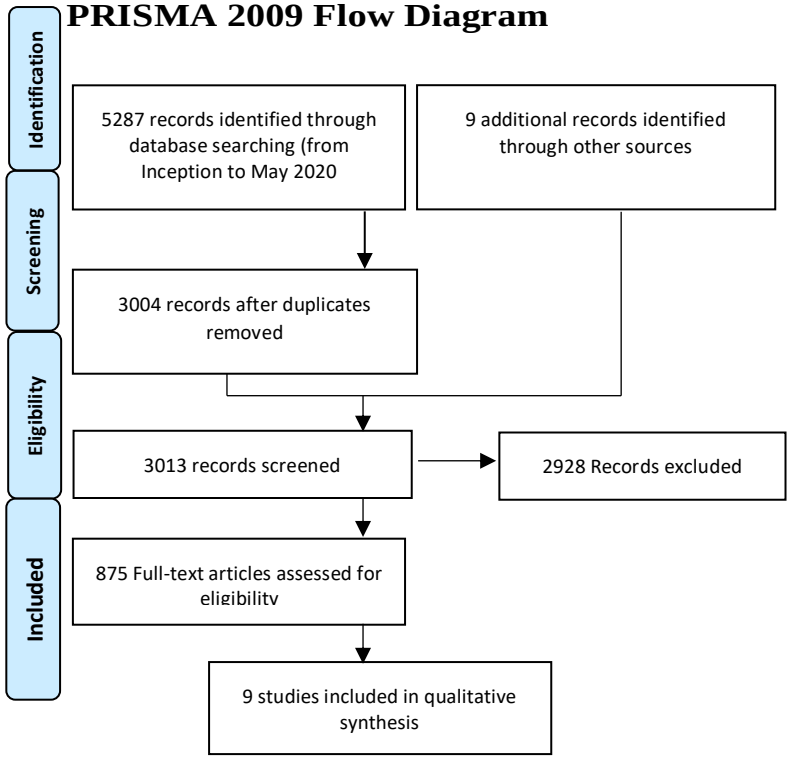


Table 1. Basic Characteristics of the Included Clinical Trials

Study ID	Sample Size	Pathology	Intervention vs. Control	Melatonin Dosage	Duration	The presence/ absence of a significant difference in the results of Melatonin and Placebo
Cavalcante [38] 2012	36	Chronic Obstructive Pulmonary Disease	Melatonin, Placebo	3 mg	3 months	Yes
Alamili [39] 2014	12	An Experimental Human Sepsis Model.	Melatonin, Placebo	100 mg	1 day	Yes
Alamdari [40] 2014	44	Inflammatory and Oxidative Stress in obese women	Melatonin, Placebo	6 mg	40 days	Yes
Hernández-Velázquez [41] 2016	37	Acute Inflammatory Response Associated With Endoscopic Retrograde Cholangiopancreatography	Melatonin, Placebo	50 mg	1 day	No
Zhao [42] 2018	60	Brain Ischemia	Melatonin, Placebo	6 mg	6 days	Yes
Sánchez-López [43] 2018	36	Relapsing-Remitting Multiple Sclerosis	Interferon β-1b and Melatonin, Placebo	25 mg	6 months	Yes
Yosefifard [44] 2019	50	Multiple Sclerosis	Interferon and Melatonin, Placebo	3 mg	24 weeks	Yes
Panah [45] 2019	40	Renal Ischemia in Transplant Patients	Melatonin, Placebo	3 mg	?	Yes
Bazyar [46] 2019	50	Diabetes Mellitus and Periodontitis	Melatonin, Placebo	6 mg	?	Yes

Study ID	TNF-α	IL-1β	IL-1Ra	IL-2	IL-6	IL-12	IL-8	IL-4	IL-10	CD44	CD133	YKL-40	Number of parameters	Melatonin Dosage	Duration	Effectiveness
Cavalcante [38] 2012	0	0	0	0	0	0	1↓	0	0	0	0	0	1	3 mg	3 months	P = 0.01
Alamili [39] 2014	1-	1↓	1-	0	1-	0	0	0	1-	0	0	1↓	6	100 mg	1 day	IL-1β P < .01; P < .05
Alamdari [40] 2014	1↓	0	0	0	1↓	0	0	0	0	0	0	0	2	6 mg	40 days	TNF-α p = 0.02; IL-6 p = 0.03
Hernández-Velázquez [41] 2016	1-	0	0	0	1-	0	0	0	0	0	0	0	2	50 mg	1 day	P >.05

Zhao [42] 2018	1↓	0	0	0	1↓	0	0	0	0	0	0	0	2	6 mg	6 days	P < 0.05
Sánchez-López [43] 2018	1↓	1↓	0	0	0	0	0	0	0	0	0	0	2	25 mg	6 months	p < 0.05
Yosefifard [44] 2019	1 -	1↓	0	0	0	0	0	0	0	0	0	0	2	3 mg	24 weeks	TNF-α p < 0.08; IL-1β p < 0.039
Panah [45] 2019	1↓	0	0	0	0	0	0	0	0	0	0	0	1	3 mg	?	P < .001
Bazyar [46] 2019	1↓	0	0	0	1↓	0	0	0	0	0	0	0	2	6 mg	?	IL-6 p = 0.008

Table 2. Measurement of RCTs and evidence of effectiveness

- **: no parameter change;**
- ↓ **: decrease of levels.**

DISCUSSION

Statistical analysis of the research summary table is performed as follows:

The original table (Table 2) has been recoded into a form suitable for analyzing in IBM SPSS, according to the following rules:

a. The target field "Effectiveness" (the presence of statistically reliable differences between groups, taking placebo and melatonin): 1 - there is a reliable difference; 0 - there is no reliable difference;

b. The input variable - any of the parameters of RCTs, if not measured, the code "-1" is assigned; if measured but not changed, the code "0" is assigned; if measured and changed (in all the cases considered there is only a decrease), the code "1" is assigned;

c. The input variables are not exposed to recoded - "Melatonin dose" and "Duration".

Thus, the table for the analysis acquires the following format (Table 3).

Table 3. Statistical analysis

TNF-α	IL-1β	IL-1Ra	IL-6	IL-8	IL-10	CD44	CD133	YKL-40	Melatonin Dosage, mg	Duration, days	Effectiveness
-1	-1	-1	-1	1	-1	-1	-1	-1	3	90	1
0	1	0	0	-1	0	-1	-1	1	100	1	1
1	-1	-1	1	-1	-1	-1	-1	-1	6	40	1
0	-1	-1	0	-1	-1	-1	-1	-1	50	1	0
1	-1	-1	1	-1	-1	-1	-1	-1	6	6	1
1	1	-1	-1	-1	-1	-1	-1	-1	25	180	1
0	1	-1	-1	-1	-1	-1	-1	-1	3	168	1
1	-1	-1	-1	-1	-1	-1	-1	-1	3	-	1

1	-1	-1	1	-1	-1	-1	-1	-1	6	-	1

Note. IL-2; IL-12; IL-4 - excluded from the consideration as unmeasured in any of the studies included in the review.

2. To assess the evidence generalized linear mixed models (GLMM) used [47]. This type of models provides a high flexibility in the process of generating and studying new hypotheses because correlations are sought at the level of average values of variables, their variances and covariances. GLMM has been implemented as an appropriate procedure of the IBM SPSS Statistics package.

The criteria of selecting this qualitative statistically sound model are: information criteria (Akaike and Bayes), as well as both the statistical significance of the model as a whole and of the model variables (in our case $p < 0.05$). Thus, we have been tested all the possible hypotheses and combinations of the variables until the statistically significant model and all its independent variables have been found. The fixed (core) effects are represented by all the input variables: all the measured parameters of RCTs are the main 1-factor effects; "Dose" and "Duration" are represented by a 2-factor effect, as it is assumed that there is a possible cumulative effect of the drug. The general characteristics of the model are presented in Fig. 3.

Draw attention the high classification qualities of the constructed model: overall accuracy - 100%; accuracy of classifications "Effectiveness" - 100% (Fig. 4).

The variables that were included in the model and determine its accuracy: absence of measurement of the "IL-1Ra" indicator; measurement and absence of changes in the "IL-6" indicator; a free term (see Fig. 5).

Figure 3. General characteristics of the model

Model Summary

Target: Effectiveness

Target		Effectiveness
Measurement Level		Nominal
Probability Distribution		Multinomial
Link Function		Generalized logit
Information Criterion	**Akaike Corrected**	126.000
	Bayesian	15.381

Information criteria are based on the -2 log likelihood (0.000) and are used to compare models. Models with smaller information criterion values fit better.

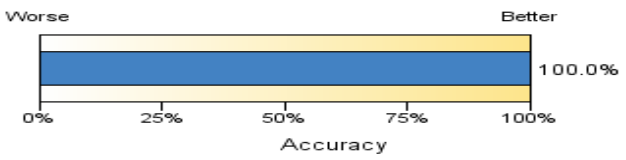


Figure 4. Model classification qualities

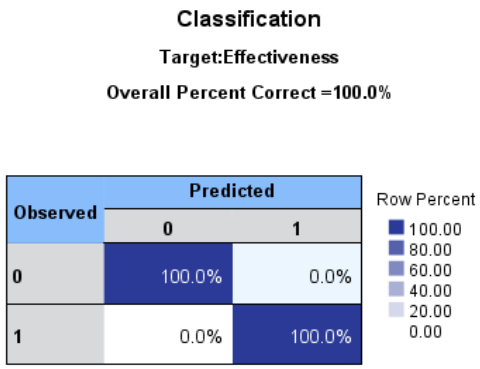
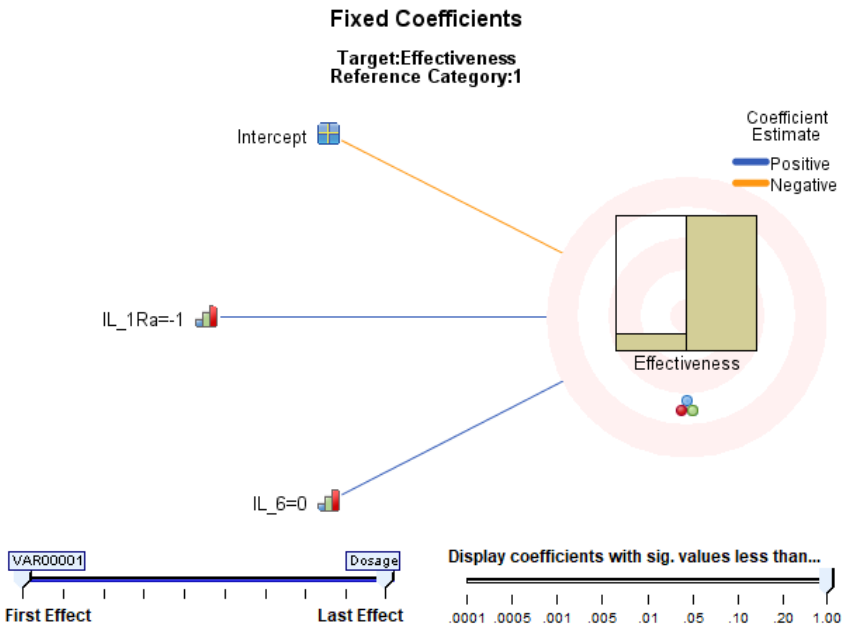


Figure 5. Assessment of immunological effects of melatonin



CONCLUSION

We have found out that melatonin has significantly improved the state of the immune system in all the trials (heterogeneity P <0.05). The effects are consistent in terms of the melatonin dose, the duration of the treatment, and the baseline immune status. No serious adverse events have been reported. The considerable immunomodulatory effect, low side effects and low costs, associated with this intervention, substantiate the great potential of melatonin in the treatment of diseases accompanied by immunodeficiency. The confirmation of the immunomodulatory effect and safety of melatonin in diseases associated with such conditions will require blind independent RCT with the usage of a wider range of immunological parameters.

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Address for communication:

ASSESSMENT OF IMMUNOLOGICAL EFFECTS OF MELATONIN IN IMMUNODEFICIENT POPULATION: A SYSTEMATIC REVIEW OF RANDOMIZED CONTROLLED TRIALS

Diana Dorosh

V. N. Karazin Kharkiv National University, School of Medicine, Department of General and Clinical Immunology and Allergology.

Svobody Square, 6, Kharkov, Ukraine, 61022.

E-mail: diana.dorosh@karazin.ua