Original Article

Serum Melatonin Level in Patients with Rheumatoid Arthritis: A Systematic Review and Meta-analysis

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Abstract

Objective: Melatonin is the major secretory product of the pineal gland and may play a role in the etiology and clinical symptoms of rheumatoid arthritis (RA). This systematic review and meta-analysis were conducted to determine the morning serum melatonin level in patients with RA compared to non-RA patients.

Materials and Methods: We searched English databases (PubMed, Web of Science, Scopus, and Google Scholar) for observational studies regarding the morning serum melatonin level in RA patients from January 2000 to October 2020. The weighted mean difference (WMD) was assessed. Heterogeneity was analyzed using the Q Cochrane test and the I^2 measure. To assess the relationship between covariates and effect size, we performed a meta-regression analysis. Furthermore, we used the Egger test alongside the funnel plot for the assessment of publication bias.

Results: The literature search revealed 214 studies, of which 7 studies met the eligibility criteria. We did not find heterogeneity (I^2 = 0.0%). This study showed a higher level of morning serum melatonin levels in RA patients in comparison with the controls (WMD = 5.85). In meta-regression analysis, none of the variables had a significant relationship with the efficacy of effect size. The funnel plot showed all the included studies were symmetrically distributed in the triangle area. Egger's test also showed an absence of publication bias.

Conclusions: Melatonin levels were higher in RA patients than the controls, but due to the small sample size of included studies, the power of this meta-analysis was low.

Key Words: *Meta-analysis, observational studies, rheumatoid arthritis, serum melatonin level*

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disorder that results in pain, stiffness, joint swelling, and deformity of joints.[1] RA affects nearly 1% of the world's adult population, while between 5 and 50 per 100,000 people newly develop the condition each year.[2]

RA is usually associated with a circadian rhythm for symptoms like morning stiffness.[3] The other RA symptoms, such as joint pain and functional disability, are commonly observed in the early morning, and it is due to alterations in neuroendocrine and immune/inflammatory activities.[4] It seems that alteration in the function of the pituitary gland is an important factor in the circadian nature of the symptoms of RA.[5] Melatonin is the major secretory product of the pineal gland during the night and has multiple activities, including the regulation of the circadian and seasonal rhythms, antioxidant and anti-inflammatory, and anti-apoptotic effects.[6]

Melatonin has a midnight peak and a decline before the time of light onset. Therefore, endogenous melatonin may play a role in the etiology of RA.[7] Cutolo *et al*.,[4,8-10] have proposed that peak secretion of melatonin in RA patients usually is done earlier, in comparison with the controls.[8,9] Previous primary studies have shown a higher serum melatonin level in RA patients compared with the controls.[3,11] However, there is a contrast in serum melatonin levels in RA patients.[12] A previous study has shown that melatonin through inhibition of the proliferative

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activity of fibroblast-like cells in synovial, diminishes the activity of RA.[13] However, it has been shown that melatonin can increase inflammation in synovial fluid in RA by impairing the production of interleukin 12 (IL-12) and nitric oxide,[14] interferon-gamma (IFN-γ), IL-1, and IL-6.[15] It seems melatonin has a more pro-inflammatory role than an anti-inflammatory role.[15,16] Melatonin also has an inhibitory effect on matrix metalloproteinase-9 (MMP), which leads to joint destruction in RA patients.[15] Therefore, in spite of the general antioxidant characteristics of melatonin, it has adverse effects on the pathogenesis of RA.[15,17]

It has been shown that there is an interaction between inflammation and the circadian clock.[18] Results of a study conducted by Yoshida *et al*. showed that activation of the immune system counteracts infection and increases resistance to pathogens by inducing slow-wave sleep, presumably via the production of inflammatory cytokines such as TNF-α, IL-2, or IFN-γ that are known to induce such sleep.[15] Sleep disorders are common in RA patients, and they usually have reduced effective sleep.[19] In addition, it has been reported that more RA disease activity is associated with more sleep disorders, especially in women of higher ages.[15] In this regard, it has been indicated that shift works are associated with the risk of RA in women.[20] Therefore, it seems that the body clock has a detrimental effect on the symptoms of RA and also involves in the pathogenesis of this disease.[15,16]

To the best of our knowledge, there is no systematic review and meta-analysis regarding the relationship between serum melatonin levels and RA. Therefore, this systematic review and meta-analysis were performed to have a more in-depth understanding, to summarize evidence relating the serum melatonin levels and RA, and to find the best approach for managing the disease. The purpose of this study was to conduct a systematic review and meta-analysis to determine the morning serum melatonin level in patients with RA compared to the non-RA patients.

Materials and Methods

Criteria for including studies

All analytical observational studies (case-control and cross-sectional studies), evaluating both men and women suffering from RA of any ethnic background and nationality, were included. Criteria for RA were diagnosed based on the American College of Rheumatology (ACR) classification criteria. Primary studies with participants older than 70 years, or those who suffer from liver disease or chronic sleep disorders, or those who had excess dietary caffeine or ethanol were excluded.

We included just melatonin levels in serum, and measurement of melatonin in urine or tissues was excluded. All animal studies and also *in vitro* and interventional studies were excluded.

Research strategy and selection of studies

This systematic review and meta-analysis were conducted based on preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines.[21] We searched English databases (PubMed, Web of Science, Scopus, and Google Scholar) for observational studies regarding the morning serum melatonin level in RA patients from January 2000 to October 2020. We also used references of included primary articles, key journals, and ACR guidelines manually for search. A search was carried out, using the following keywords and terms: "melatonin" AND "RA."

Data extraction

The primary citations obtained during the database survey were recorded in a text file, according to their topics and abstracts. Following an initial screening, especially eligible records were selected for full-text download. The final eligibility and inclusion criteria for the downloaded full texts were appraised by 2 separate investigators at three levels: Title, abstract, and full text. Afterward, 2 authors extracted the requisite data. When the reported data were insufficient or ambiguous, we contacted the corresponding author by E-mail to request additional information. After three E-mails with a week interval, the study was excluded. Authors have independently assessed the risk of bias in the included studies, according to the criteria from the modified STROBE checklist, as a validated method for assessing the quality of observational and case-control studies.[22] The instrument used a system to evaluate case-control studies based on some criteria: Title and abstract, background, objectives, study design, setting, participants, variables, data sources, and measurements, bias, study size, quantitative variables, statistical methods, participants' result, descriptive data result, outcome data and main results, other analyses, key results, limitations, interpretation, and generalizability.[22]

For each domain, the following description was used for management of the risk of bias: "Yes," "No" and "Unclear." We graded the quality of included studies and risk of bias, using grading 1 for "yes" and 0 for "no and unclear," and disagreement was resolved by discussion.

Finally, the following properties of each related study were extracted: First author, year of publication, country, study population, study design, latitude, duration of study, number of cases, number of controls, time of assay, serum melatonin level in cases (mean and standard deviation [SD]), serum melatonin level in controls (mean and SD), duration of disease (mean and SD), melatonin assay method, kind of administered drug, age distribution in cases (mean and SD), age distribution in controls (mean

and SD), study quality, season of sampling, and disease activity score (DAS).

Statistical analysis

All analysis was performed using Stata version 11.1 (StataCorp., College Station, TX, USA). For continuous data, the weighted mean difference (WMD) and standardized mean difference (SMD) were assessed by the Cohen method.[23] For assessing the potential predictors of effect size measure, we used meta-regression analysis with various factors (independent variable) such as latitude (geographical area of study location), kind of administered drug, methodological quality score, duration of the study, disease duration, gender and mean age of cases and control group. We used Random Effect Model and DeSimonian-Laird method[24] for combining the effect size measures. The statistical heterogeneity was assessed using the Q Cochrane test and the I^2 measure, which estimates the proportion of variability between studies that is due to inter-study heterogeneity rather than chance.[25] In addition, due to the small number of primary studies (<10 studies), we used the Egger test alongside the funnel plot for the assessment of publication bias.[26] Finally, for estimating the number of missing studies, we performed the Trim and Fill test. Statistical significance was defined as a $P < 5\%$.

Results

Selection of studies

From the 214 identified articles, 7 were included, and the results from these studies were weighted [Table 1].[3,7,8,11,27-29] A total of seven studies involving 234 participants met the eligibility criteria. They were all published between 2002 and 2014, and compared serum melatonin levels in RA between controls and RA patients. A PRISMA flowchart showing the search and study selection strategy is presented in Figure 1. The detailed information presented in the 7 included studies is summarized in Table 1.

Of the three studies based on the Asian population, one was based on the Turkish population[7] and the other two on the Iranian population.[3,27] One study was based on the African (Egypt) population,[28] and three studies were based on the European population: Two studies in Italy[8,11] and one in Estonia.[29] We assessed the quality of the primary studies using a modified STROBE checklist, as shown in Table 2. There was a variety in quality work of studies based on the STROBE checklist. Some studies had high quality,[3,27,29] and some had moderate[8,28] or even low quality[7,11] [Table 1]. All studies investigated the serum melatonin level at 8 am in RA patients and controls. All primary studies were individually matched for gender variable. In all studies, participants were adults, except in one that the mean age of the participant was

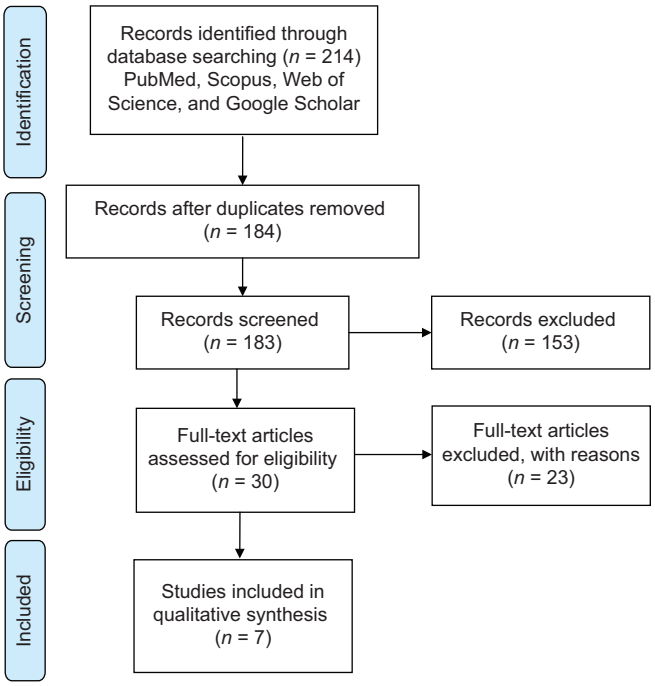

Figure 1: The preferred reporting items for systematic reviews and meta-analyses flow diagram of the literature search process

15-year-old (recognition of the disease in all studies was based on the ACR criteria). In all studies, the collection of blood samples was done at about the same period (8 am) in cases and controls. Investigators in all studies used either enzyme-linked immunosorbent assay or radioimmunoassay for the determination of the level of melatonin in serum samples [Table 1]. All studies reported levels of melatonin as mean SDs, except the study conducted by Sulli *et al*.[11] Therefore, we used the web plot digitizer platform[30] for extracting the numerical data (mean and SD). The season of blood sampling was winter in four studies,[7,8,27,29] summer in one study,[3] unclear in the other one,[11] and both winter and spring seasons in the other study[28] [Table 1]. There were high varieties of the kind of administered drug in these 7 included studies. In four studies, patients received disease-modifying anti-rheumatic drugs (DMARDs).[3,7,27,28] In three studies, the patients did not receive DMARDs;[8,11,29] however, they received just nonsteroidal anti-inflammatory drugs (NSAIDs). In one study, patients used 3 types of drugs: DMARD steroids (methotrexate) and NSAIDs (prednisolone and ibuprofen).[28] In three studies, patients received both DMARDS and steroids [Table 1], DAS was 2.3 ± 1.10,[28] 1.9 ± 0.92,[3] and 2.3 ± 0.73[27] and there was no information about them in the other included studies [Table 1]. Except for 2 articles,[3,27] most of the included articles had not information about clinical characteristics of RA patients such as rheumatoid factor, anti-citrullinated protein antibodies, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), full blood count complete blood count, X-ray imaging and

Table 1: The characteristics of included studies

	First author/Reference						
	Baykal 2013[7]	**El-Awady *et al.* 2007[28]**	**Afkhamizadeh 2014[3]**	**Afkhamizadeh *et al*., 2012[27]**	**Otsa *et al*., 2004[29]**	**Cutolo 2005[8]**	**Sulli 2002[11]**
Country	Turkey	Egypt	Iran	Iran	Estonia	Italy	Italy
Study population	54	41	40	40	29	14	16
Study design	Case-control	Case-control Cross-sectional	Case-control Cross-sectional	Case-control Cross-sectional	Case-control Cross-sectional	Case-control Cross-sectional	Case-control
Latitude	39.9	30.07	36.20	36.20	59.26	59.26	44.25
Duration of study (months)	6	6	6	6	3	3	-
Number of cases	29	21	30	30	19	14	10
Number of controls	25	20	10	10	10	14	6
Time of assay	8 am	8 am	8 am	8 am	8 am	8 am	8 am
Serum melatonin level in case pg/mL, mean±SD	15.40±10.12	13.9±8	30.25±52.4	30±46.8	25.8±43.5	4.7±5.3	18.03±7.05
Serum melatonin level in control pg/mL, mean±SD	10.03±5.85	8.1±2.7	11.23±13.8	16.4±16.4	2.7±119	25.8±43.5	9.89±8.18
Duration of disease, mean±SD	6.4±0.6 Year	6.9±4.9 Year	6.4±4.3 Month	5.4±5.3 Month	4±3 Year	4±3 Year	4±2 Year
Melatonin assay method	ELISA	ELISA	ELISA	ELISA	RIA	RIA	RIA
Kind of administered drug	DMARDs + prednisolon	DMARDs + prednisolone + ibuprofen	DMARDs + prednisolon	DMARDs + prednisolon	NSAIDs + antacid	NSAIDs	NSAIDs
Age distribution in controls, mean±SD	47.8±0.7	15.3±5.6	37.7±8.7	45.9±3.6	50±15	66±5	50±18
Age distribution in cases, mean±SD	49.4±0.8	15.2±5.5	43.4±12.9	51±13.3	51±14	66±7	57±13
Study quality	14	16	24	24	22	20	9
Season of sampling	Winter	Winter-spring	summer	Winter	Winter	Winter	-
DAS	--	2.3 (1.10)	1.9 (0.92)	2.2 (0.73)	-	-	-

SD: Standard deviation, ELISA: Enzyme-linked immunosorbent assay, RIA: Radioimmunoassay, DMARDs: Disease-modifying anti-rheumatic drugs, NSAIDs: Nonsteroidal anti-inflammatory drugs, DAS: Disease activity score

Table 2: The meta-regression analysis of serum melatonin level with different factors

Factor	Coefficient	*P*	95% CI	Residual I^2 (%)	Adjusted R^2
Study quality	-0.030275	0.33	-0.1026083-0.0420583	0.00	.%
Latitude	-0.010843	0.54	-0.0536272-0.0319412	0.00	.%
Sampling season	0.2614890	0.47	-1.6561568-1.179137	0.00	.%
Kind of administered drug	0.2119328	0.49	-0.5206562-0.9445217	0.00	.%
Mean age of cases	-0.0143423	0.24	-0.0463584-0.0176739	0.00	.%
Duration of study	0.1442692	0.53	-0.6913769-20189376	0.00	.%
Duration of disease	-0.0368597	0.51	-0.2402666-0.1665471	0.00	.%
Gender of cases	0.5707955	0.022	0.1327675-1.008824	0.00	.%

CI: Confidence interval

information about monitoring remission of RA, and also a clear definition about DAS. Therefore, no evaluation was performed in the present study.

Results of statistical analysis

The combined or overall SMD was 0.59 (95% confidence interval [CI]: 0.31–0.87). We found the lowest heterogeneity in serum melatonin levels, among the 7 included studies (I squared = 0.0%, *P* = 0.7) [Figure 2]. Effect sizes suggest that RA patients have higher serum melatonin levels than controls, and WMD was estimated at 5.85 pg/mL (95% CI: 3.46–8.24) [Figure 2].

Table 2 shows the results of meta-regression analysis for the assessment of the relationship between various variables with effect size. Meta-regression analysis results showed that among different variables, none of them had a significant relationship with the efficacy of effect size.

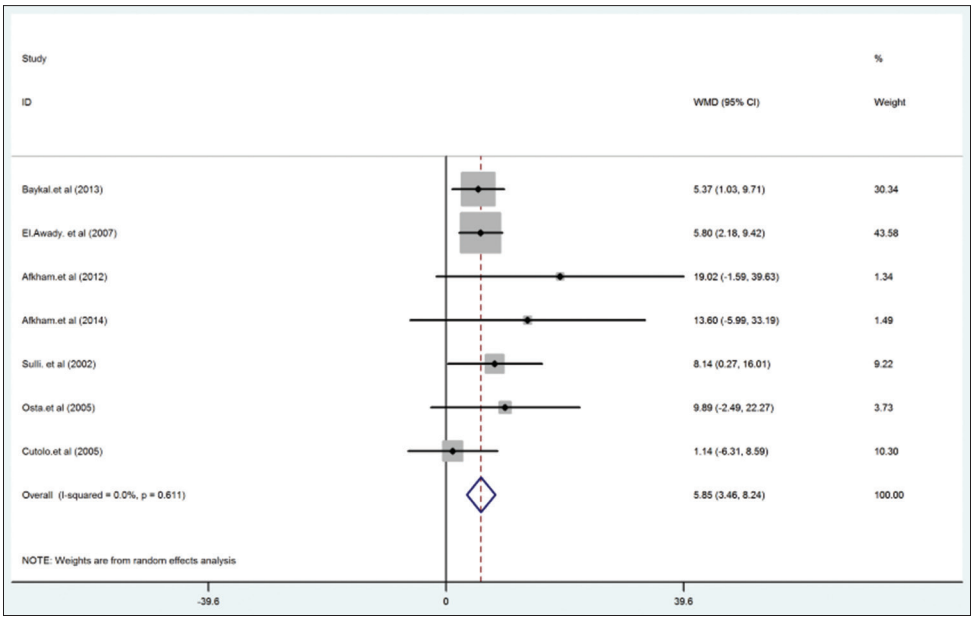

Figure 2: The meta-analysis of included studies assessing the serum melatonin level in controls and rheumatoid arthritis patients

Meta-regression analysis showed only gender distribution in the case group, such as increasing of female to male ratio, which was related to the effect size measure and attenuated the effect size measure [Table 2].

Egger's test also showed an absence of publication bias (coef = −0.4616102 and *P* = 0.76) [Figure 3]. The result of the Egger test showed that bias was negligible because it was not meaningful. Due to the results of the Fill and Trim test, we did not add a study, so there was no bias.

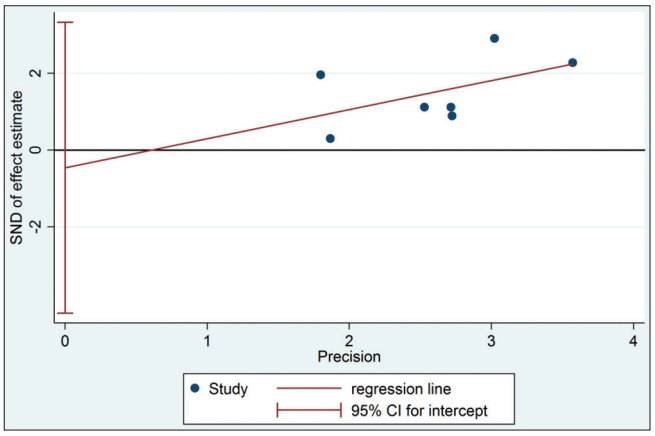

Figure 3: The Egger's test of the serum melatonin level in rheumatoid arthritis patients

Discussion

The present systematic review and meta-analysis summarized the results of 7 studies related to the serum melatonin level. The results showed a higher level of melatonin in serum samples of patients with RA, in comparison with controls at 8 am and based on Cohen's classification,[23] the magnitude of the relation between serum melatonin level and RA occurrence was moderate to high. Previous studies have shown an increased level in serum values of melatonin in RA patients compared with the controls.[3,11] In contrast, West and Oosthuizen. in 1992 showed a decreased level of serum melatonin levels in RA patients.[12] The WMD is an unstandardized effect size measure and similar to the mean difference (MD). MDs in the primary study level are combined based on the individual study weight and estimated as WMD. Therefore, WMD could show the clinical importance of the assessed parameter. In the present study, WMD was obtained at 5.85. It has been shown that melatonin can increase inflammation in synovial fluid in RA by impairing the production of IL-12 and nitric oxide,[14] INF-γ, IL1, and IL6.[15] It seems melatonin has a more pro-inflammatory role than an anti-inflammatory role.[15,16] Melatonin also has an inhibitory effect on matrix MMP-9, which leads to joint destruction in RA patients.[15] Therefore, in spite of the general antioxidant characteristics of melatonin, it has adverse effects on the pathogenesis of RA.[15,17] In general, the role of melatonin in the destruction of joints needs further investigation.

We did not find heterogeneity (I^2 = 0.0%). A meta-analysis with I^2 = 0 means that all variability in effect size estimates is due to sampling error within studies. Different sampling in every study leads to sampling error.[31] In our study, also there was a variety in the sampling in each study.

The results of meta-regression analysis in the present study showed that the relationship between serum melatonin and female cases of RA is more important than male patients. However, due to insufficient study numbers, we could not rely on the meta-regression findings regarding

the other potential factors. It has been shown that melatonin secretion is altered in the light cycle. It is well known that clinical signs and symptoms of RA are different during a day, between days, and the morning joint stiffness observed in almost all patients with active RA is also considered one of the most peculiar diagnostic criteria of the disease.[4] Similarly, other RA symptoms, such as joint pain and functional disability, are more severe in the early morning and are a consequence of altered neuroendocrine and immune/inflammatory activities.[4] In 2002, Sulli *et al*. demonstrated in patients with RA and controls, melatonin levels increased progressively from 20:00 to the early morning hours, and it reached a peak level at midnight in patients with RA, which was at least 2 h and earlier than in healthy controls.[11] Melatonin production and psychopathology levels have seasonal fluctuations, and these variations should be taken into account when investigating in this field.[32] It seems that the human pineal gland is more sensitive to light inhibition in the late winter than in the summer.[31] However, in the present study, there was not a significant relationship between the season of study with the efficacy of effect size (coef = 0.26, *P* = 0.4), which may be due to low numbers of related articles.

The present study showed that an increase of 10° latitude (moves from the equator toward the poles) can reduce the power indicator effect size measure by about 0.1 unit (coeff = −0.01, *P* = 0.5); however, it was insignificant. In this regard, Weydahl *et al.* in 2001 showed that geomagnetic activity influences the melatonin secretion at a latitude that is 70 degrees north of the Earth's equatorial.[31] In the present study, the latitude in different studies was in the range of 36.20–59.26, and maybe this is the reason that latitude was not effective in modifying the heterogeneity. Previous studies have shown differences in the prevalence of RA in north Europe and other Mediterranean countries such as 1.96% in Finland, 1.1% in England, 0.9% in Sweden, Denmark, and the Netherlands, 0.2% in Greece, 0.3% in Italy, and 0.3% in Israel.[33]

The peak endogenous melatonin level is significantly higher in younger people than the older.[34,35] In this study, the range of age in both controls and cases was between 15 and 66 years. Every one unit in the mean age of cases or controls corresponded to a decrease of 0.01 unit in effect size (*P* = 0.2). Although age is considered to affect the level of melatonin secretion, in the current study, there was not a significant relationship between the mean age in cases and controls with the efficacy of effect size. Maybe it is due to the range of ages that was less than seventy. It has been shown that in human studies, melatonin secretion is declined significantly at the age of seventy or more.[34,35]

The current study showed that every one degree in quality of study corresponded to a reduction of about 0.3 units in effect size. However, it was not significant (coef = −0.30, *P* = 0.3). Maybe it is due to the performance of the 7 included studies in a close range of years, from 2002 to 2014, as all of them were after 2000. Although the duration of disease was not equal in our studies, it could not modify the heterogeneity. It has been shown that melatonin level is higher in newly diagnosed RA, compared to those who had the disease for a long time.[3]

In the 7 included studies, there was a variety in the type of administered drugs to the RA patients. There is an interaction between inflammation and the circadian clock; therefore, damage or disruption of the clock resulted in a significant effect on the immune system activity, with a probable effect on the pathogenesis of RA.[4] It was reported that serum TNF-α was higher in RA patients than the controls and correlated with the higher serum melatonin level in Estonia.[8] Since different cell populations involved in the inflammatory process are particularly activated during the night, therapeutically approaches used in RA, for example, conventional DMARDs and NSAIDs, and glucocorticoids, can be used for the same concepts of chronotherapy.[4] In our study, a variety of DMARD combination therapy[3,7,27,28] or NSAID therapy[8,11,29] was observed. West and Oosthuizen in 1992 showed a lower morning plasma melatonin concentration in healthy controls, treated with indomethacin.[12] There is no information about the interaction between endogenous melatonin with NSAID, DMARDs, or glucocorticoids. However, melatonin is considered a powerful endogenous free radical scavenger, but its increasing level in RA patients is associated with inflammatory markers; therefore, melatonin is considered as a pro-inflammatory hormone in RA patients.[4,36] It has been shown that melatonin treatment increases T-lymphocyte proliferation.[37] Melatonin may be synthesized and be released by activated human T-lymphocytes.[34] In our review, receiving various drugs by patients was not associated with effect size (coef = 0.21 *P* = 0.4).

In the current study, all patients in all included studies were in their active class; however, the enrolled articles did not include the mean value of the DAS and its component, except for three studies.[3,27,28] Afkhamizadeh *et al*. showed an absence of association between DAS and its components (especially ESR and visual analogue scale) and serum melatonin level.[3,27] Likely Forrest *et al*. reported that ESR is not decreased after treatment with melatonin.[38] However, El-Awady *et al*. reported a positive correlation between DAS of juvenile RA and ESR and CRP, and they also showed a positive significant correlation between DAS and melatonin level.[28]

Strengths and limitations of study

Our analysis has specific strengths and limitations. A major strength in our study was the application of advanced techniques of statistical analysis that allowed summarizing all included studies to compare serum melatonin levels

between RA patients and controls. A limitation was in the number of included studies. We just used 7 studies; therefore, we could not perform a subgroup analysis for assessing the heterogeneity. In this condition, the power of both meta-analysis and therefore, meta-regression analysis was pretty low. The design of the study in all papers was case–control or cross-sectional; therefore, recall bias and selection bias was inevitable.

The other limitation was the small sample size in both cases and controls and the lack of different age groups. Furthermore, the absence of complete information about the mean value of the DAS and its component was another important limitation in the present study.

The study of El-Awady *et al*. was conducted in Egypt that is considered an Asian-African country.[28] Also, the study of Baykal *et al*. was performed in Turkey that is considered an Asian-European country.[7] In the present study, most populations were from Asia and Europe, and the other populations such as America, Australia, New Zealand, and also Africa were not included. Therefore, the origin of the population is considered another cause of limitation. The other limitation was the lack of enough information about serum melatonin alterations or peak at other times. We studied melatonin concentration just at 8 am, which is not a surrogate of the circadian manner of melatonin secretion. Therefore, additional studies that cover the abovementioned gaps are needed.

Conclusions

This study showed a higher level of serum melatonin level at 8 am in RA patients compared with the controls with the absence of heterogeneity and lack of publication bias. It showed that probably all included studies have had pretty consistency in their methodology and there was sampling error variability in every single study. Melatonin levels have been found higher in RA patients than the controls, but due to the small sample size of included studies, the power of this meta-analysis was low.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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