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Serum Level of Melatonin and Severity of Coronary Artery Diseases

Hamidreza Rashidinejad, M.D.[1], Hamidreza Nasri, M.D. [1], Mohammad Ali Pour Ahmadi, M.D.[2], Mansour Moazenzadeh, M.D.[3]

1- Associate Professor, Cardiovascular Research Center, Institute of Basic and Clinical Physiology Sciences, Kerman University of Medical Sciences, Kerman, Iran

2- Cardiovascular Research Center, Physiology Research Center, Institute of Neuropharmacology, Kerman University of Medical Sciences, Kerman, Iran

3- Associate Professor, Cardiovascular Research Center, Institute of Basic and Clinical Physiology Sciences, Kerman University of Medical Sciences, Kerman, Iran (Corresponding author: Email: mmoazenzadeh170@gmail.com)

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Abstract

Background: Coronary Artery Disease (CAD) as a complex process will be the most common cause of death in the world by 2020. One of the relatively new factors associated with CAD is the plasma level of melatonin. This study aimed to determine the effect of plasma melatonin level on the occurrence and severity of CAD.

Methods: This cross-sectional study was conducted from August to December 2018 in Kerman, Iran. Eighty-seven adolescents with suspected CAD were selected via the convenience sampling method. Severity of CAD was evaluated by a cardiologist for each patient using Gensini score. The anxiety, depression, and sleep disturbance of participants were examined by HADS and PSIQ questionnaires, respectively. The blood sample of patients was taken at 3:30 a.m. and it was immediately transferred to the laboratory for serum separation. A two-part model was used for data analysis using STATA software.

Results: The mean age (±SD) of the participants was 54.0 (±10.83) years. Less than half of the patients experienced anxiety and depression symptoms during last month (33% and 42%, respectively). Results showed that more than half of the patients (n=51, 57.5%) were diagnosed as CAD patients. According to multivariate regression models, melatonin (AOR=0.96, 95% CI: 0.94, 0.98) and depression (β: 0.79, 95% CI: 0.06, 1.52) were determined as predictors for CAD occurrence and severity, respectively.

Conclusion: Melatonin as a protective factor has an effect on the occurrence and severity of CAD, but the existence of some diseases like mental disorders can lead to a decrease in the plasma concentration of melatonin. By treating depression and improving melatonin synthesis and secretion cycle, the occurrence and severity of CAD may be decreased.

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Introduction

Coronary artery disease (CAD) is a complex process which starts from childhood and shows its symptoms during the progressive sequence in the middle age or aging. In epidemiological investigations, it is suggested that this disease will be the most common cause of death

in the world by 2020 (1). CAD has attracted the attention of many researchers to the point that this process is a multifactorial process created as a result of the interaction between metabolic and cellular factors. One of the relatively new factors associated with coronary heart disease (CHD) is the plasma level of melatonin. Melatonin is a hormone which is produced in the pineal gland. It is soluble in water and fat, and as it is not stored in the pineal gland, its values in serum indicate gland activity (2).

Several studies have been conducted concerning the beneficial effects of melatonin on the cardiovascular diseases (3-5). Melatonin has a protective effect against ischemic injury by reducing the sympathetic tone and rhythmic changes in heart rate, blood pressure, and cardiac output (6). In addition, melatonin increases collagen scar caused by myocardial ischemia and its strength through direct effect on fibroblasts (3). Melatonin might be involved in the reduction of cardiac hypertrophy and the prevention of heart failure. A great deal of evidence suggests that melatonin plays a role in important processes of the body including the regulation of body fluids, acid-base and nitrogen balance (7).

Various studies have shown a reduction in plasma melatonin level and the risk of CAD. These studies showed that the plasma level of melatonin decreased in patients with CAD (8-11).

Down-regulation of beta-adrenergic receptors phenomenon may affect melatonin levels due to high sympathetic activity in patients with CAD (12). In a study in Iran, it was found that the prescription of melatonin has a therapeutic effect in congestive heart failure (13). The results of a study on 66 patients showed a significant reduction in nocturnal urine samples at the level 6-sulfatoxymelatonin that is a urinary metabolite of melatonin (14).

Moreover, oxidized low-density lipoprotein (LDL) due to the presence of superoxide anions and hydroxyl radicals, which play a major role in the atherosclerotic disease, are neutralized by melatonin and as a result of a reduction in melatonin, atherosclerosis is intensified (15-17). Meanwhile, melatonin acts against damages caused by reperfusion in the heart (18,19). Also, the ability to reduce arrhythmias following mediation by melatonin has been confirmed (20).

In addition, the relationship between melatonin and taking morphine, sleep disorder, night working hours, long flights, depression diseases, and anxiety that affect the sleep-wake cycle has been confirmed (21). Likewise, nocturnal melatonin level was significantly reduced in depressed patients hospitalized due to MS Attack (22).

Several studies have been done to investigate the relationship between melatonin and CAD, but the relationship between the severity of CAD and plasma melatonin level has not been clearly determined. According to the beneficial effects of melatonin on the cardiovascular system and due to the paucity of similar researches, this study was conducted to determine the relationship between the plasma level of melatonin and the occurrence and severity of CAD in Kerman, Iran.

Materials and Methods

Subjects and setting

This cross-sectional study was conducted from August to December 2018 in Kerman, South East of Iran. Using a convenience sampling, 87 adolescents with suspected CAD were recruited. These patients were admitted to the Cardiology Department of Shafa hospital in Kerman and had angiography

indication. Inclusion criteria encompassed the absence of diabetes, lack of liver disease and kidney failure, lack of addiction to opium and morphine injection, lack of night shifts and long flights, lack of NSAIDS drugs, and antidepressants and antiepileptic drugs.

Data collection

Because anxiety, depression, and sleep disturbance can change the plasma melatonin levels, the participants of this study completed three self-reported questionnaires. The anxiety and depression of participants were examined by hospital anxiety and depression scale (HADS) standard questionnaire that consists of 14 questions evaluating the symptoms of anxiety and depression during last months. A high score reveals that a person has experienced anxiety and depression symptoms more. The validity and reliability of this questionnaire have been confirmed (23,24). The second part of the Pittsburgh sleep quality index (PSQI) questionnaire was applied to assess the status of participants' sleep disturbance. Ten questions were asked in this part and a high score reflects a greater severity of sleep disturbance (25).

Melatonin assessment

All subjects were kept in a room with lights turned off to remove the light effect from 10:00 p.m. to the sampling time, and they were protected from the light presence probability using a medical blindfold. The ambient temperature of 18-24˚C for all subjects was equal and the subjects were quiet. The blood sample of patients was taken at 3:30 a.m. and it was immediately transferred to the laboratory for serum separation. Serum sample was kept at -20˚C until testing (up to three months) using ELISA method. Melatonin level was measured using enzyme immunoassay kit (GmbH, Hamburg, Germany). In the case of hemolysis icteric or lipemic, samples were excluded from the study.

Gensini score calculation

The next day, angiography was performed for subjects and angiographic films were interpreted by two cardiovascular specialists who did not know the patients. Severity of CAD was evaluated by a cardiologist for each subject using Gensini score. This rating system was presented for the first time in 1983 by Gensini (1). After determining the percentage of CAD (0-45-50-75-90-100%), its equivalent was respectively considered (0-1-2-4-8-16-32) in Gensini system. Then, based on the location of the stenosis and the involved vessel, the coefficient was considered and after multiplying Gensini score in the relevant coefficient and summing up the obtained numbers, the index of involved coronary artery that is Gensini score was recorded. Finally, patients were classified according to the Gensini score to Gensini score equals to 0-20, 21-40, 41-60, 61-80, and 81-100 (11).

Ethical approval

This study was approved by the Ethics Committee of Kerman University of Medical Sciences. Before the initiation of the study, the objectives of the research were explained to the participants and written consent was obtained from them.

Statistical analysis

Normal data such as age were described using mean (±SD), and median (IQR) for data with abnormal distribution such as Gensini score. For comparing qualitative demographic variables, Chi-square and Fisher’s exact test were used. Mann-Whitney U test and t-test were used for laboratory findings. To determine the factors associated with coronary artery stenosis,

a two-part model was used. The first model constituted of univariate and multivariate logistic regression models to determine the predicting factors of CAS occurrence. The second model was the linear regression model to assess factors associated with CAS severity. Backward method was developed for multivariate regressions in both models. All statistical analyses were done by SPSS version 23 and STATA software version 14. The P-value less than 0.05 was considered statistically significant.

Results

Out of 87 patients participated in this study, 45 (51.7%) were female. The mean age (±SD) of participants was 54.0 (±10.83) years, ranging from 20 to 73 years. Findings from laboratory data showed that the mean (±SD) of all measured indicators was in the normal range. The symptoms of anxiety during the last month were reported by one-third of the participants (n=29, p=33.3%), but nearly half of all subjects (n=37, 42.5%) experienced depression in the same period. The normal serum melatonin level was observed (n=57, 65.5%), while sleep disturbance was frequent among all of the subjects. Table 1 shows demographic characteristics and laboratory details of participants.

According to the angiographic results, more than half of the subjectsh (n=50, 57.5%, 95% CI: 47.1, 60) were diagnosed as patients with CAD. Figure 1 shows the distribution of Gensini score of patients with CAD (Median: 50, IQR:37). According to the results, normal subjects were younger than patients with CAD (P<0.05) and the concentration of melatonin was higher among them (P≥0.05). The frequency of depression was higher among patients with CAD (P<0.001); however, the frequency of sleep disturbance and anxiety disorders was not different (P=0.32, 0.40, respectively) (Table 1).

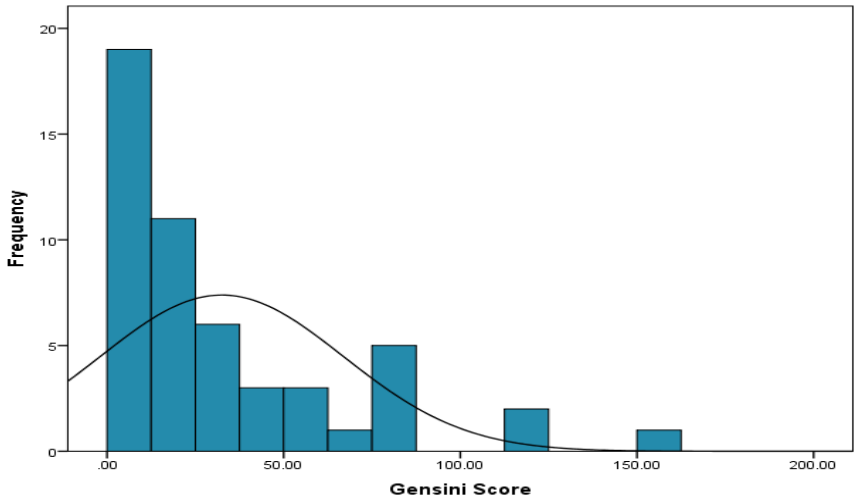

Figure 1. Distribution of Gensini score among CAS patients, Shafa hospital, Kerman, in 2018.

Table 1. The comparative evaluation of demographic and laboratory characteristics of patients suspected with CAD based on the angiography results, Shafa hospital, Kerman, 2018

Variables	Level of Variables	Total	CAD patients (n=50)	Normal Patients (n=37)	P-value
Age		54.0±10.83	56.10±8.92	51.16±12.54	0.04
Lab result	**WBC**	6618.72±2209.95	6935.10±1753.91	6191.18±2674.53	0.40
	HBG	14.49±3.65	14.85±4.47	14.01±2.06	0.26
	Urea	33.74±17.46	34.24±19.65	33.08±14.21	0.94
	Creatinine	1.12±0.26	1.70±1.35	1.65±3.44	0.14
	FBS	106.68±22.11	110.25±24.72	101.86±17.16	0.10
	Melatonin	59.19±27.44	59.49±44.26	73.41±33.96	0.02
Gender	**Female**	45 (51.7)	30 (66.7)	15 (33.3)	0.07
	Male	42 (48.3)	20 (47.6)	22 (52.4)	
Anxiety	**Normal**	58 (66.7)	31 (52.5)	28 (47.5)	0.40
	Borderline case	20 (23.0)	13 (68.4)	6 (31.6)	
	Abnormal	9 (10.3)	6 (66.7)	3 (33.3)	
Depression	**Normal**	24 (27.6)	13 (56.5)	10 (43.5)	≤0.001
	Borderline case	26 (29.9)	8 (30.8)	18 (69.2)	
	Abnormal	37 (42.5)	29 (76.3)	9 (23.7)	
Sleep disturbance	**Mild**	35 (40.2)	19 (54.3)	16 (45.7)	0.32
	Moderate	46 (52.9)	29 (63)	17 (37)	
	Severe	6 (6.9)	4 (66.7)	2 (33.3)	

The unadjusted two-part model (the first part) showed that melatonin (P≤0.01) and age (0.04) were associated with CAD occurrence and the high concentration of melatonin reduced the odds ratio of CAD occurrence (Crude Odds Ratio (COR) = 0.97, 95% CI: 0.95, 0.99), while older subjects had greater odds ratio of CAD occurrence (COR=1.04, 95% CI: 1.00, 1.08). The severity of CAD (the second part) was related to melatonin (P≤0.05), anxiety (P<0.01), and depression (P=0.01). Among patients with CAD, the severity of disease decreased with high concentration of melatonin (β: -0.01, 95% CI:-0.02, 0.00), but the severity of CAD increased by experiencing anxiety (β: 1.24, 95%CI: 0.32, 2.16) and depression (β: 0.91, 95% CI: 0.20, 1.61). Finally, based on the multivariate regression models, melatonin (AOR=0.96, 95% CI: 0.94, 0.98) and depression (β: 0.79, 95% CI: 0.06, 1.52) were determined as predictors for CAD occurrence and severity, respectively (Table 2).

Table 2. The association of some factors and the occurrence and severity of CAS among patients suspected with CAD based on the angiography results, Shafa hospital, Kerman, 2018

Variables		Occurrence of CAD		Severity of CAS	
		Crude OR[1] (95%CI)	**Adjusted OR (95%CI)**	**Crude B (95%CI)**	**Adjusted B (95%CI)**
Age		1.04* (1.00-1.08)	-	0.009 (-0.02,0.04)	-
Lab result	**WBC[2]**	0.99 (0.99-1.00)	-	0 (-0.01,0.00)	-
	HBG[3]	1.05 (0.84-1.31)	-	-0.004 (-0.17,0.16)	-
	Urea	1 (0.97-1.02)	-	0.003 (-0.01,0.01)	-
	Creatinine	2.84 (0.53-15.2)	-	-0.45 (-1.13,1.04)	-
	FBS[4]	1.02 (0.99-1.04)	1.02 (0.99-1.04)	-0.002 (-0.01,0.01)	-
	Melatonin	0.97** (0.95-0.99)	0.96** (0.94-0.98)	-0.01* (-0.02, 0.00)	-0.01 (-0.02,0.00)
Gender	**Male**	0.5 (0.21-1.18)	-	-0.4 (-1.04,0.22)	-0.59 (-1.19,0.01)
Anxiety	**Borderline case**	2.33 (0.78-6.91)	-	0.64 (-0.02,1.31)	-
	Abnormal	2 (0.45-8.77)	-	1.24** (0.32,2.16)	-
Depression	**Borderline case**	0.44 (0.14-1.39)	0.27 (0.07, 1.02)	0.33 (-0.57,1.24)	-0.02 (-0.99,0.94)
	Abnormal	2.28 (0.77-6.74)	1.70 (0.51, 5.70)	0.91* (0.20,1.61)	0.79* (0.06,1.52)
Sleep disturbance	**Moderate**	1.06 (0.43-2.59)	-	0.004 (-0.65,0.66)	-
	Severe	0.37 (0.06-2.32)	-	0.065 (-1.59,1.72)	-

1. Odds ratio
2. White blood cell
3. Hemoglobin
4. Fast blood sugar

*P≤0.05

**P≤0.01

Discussion

In the present study, patients with CAD, who were older in comparison to normal subjects, had lower plasma level of melatonin and experienced more symptoms of depression. Plasma level of melatonin was related to the occurrence and severity of CAD. The occurrence of CAD was also related to age and severity of CAD was also related to anxiety and depression disorders. Based on the findings of this study, melatonin was determined as a predictor for CAD occurrence and higher plasma concentration of melatonin significantly reduced the odds ratio of CAD occurrence. In a similar vein, depression predicted the severity of CAD and for patients with depression, the severity of disease was increased (based on Gensini score).

Based on the results, the plasma concentration of melatonin was significantly lower among patients with CAD and it was confirmed in previous studies (9-11). These studies showed that the nocturnal melatonin synthesis and secretion decreased significantly among patients with CAD. The results of the present study revealed that the plasma concentration of melatonin had an inverse relationship with the occurrence and severity of CAD and its high plasma concentration reduced the odds ratio of CAD occurrence. The severity of CAD was also decreased by high plasma concentration of melatonin. This protective role is resulted from the effect of melatonin on inflammatory process and overproduction of free radicals, which lead to vascular events (26).

The quality of sleep is one of the important factors which influences the physical and social performance of individuals (27). Melatonin plays a pivotal role on sleep quality through decreasing the sleep onset latency and increasing sleep efficiency (28). The plasma concentration of melatonin changes with increasing age, consumption of special medications, and development of diseases. This leads to poor sleep quality and sleep disturbance (29,30). Evidence shows that sleep disturbance with sleep duration could predict the risk of CADs (31). Research findings show that poor sleep quality is strongly associated with depression and is highly prevalent among patients with CAD (27,32,33). In fact, the effect of psychological disorders such as anxiety and depression on sleep quality is not clearly understood, but they have an effect on each other (32,34).

The findings of this study showed that more than half of the subjects with moderate and severe sleep disturbance were diagnosed as patients with CAD. Due to variation of melatonin concentration in some mental and physical diseases, lower concentration of melatonin among patients with CAD, who experienced more depression symptoms, leads to sleep disturbance. High prevalence of depression and sleep disturbance among patients with CAD confirmed the association between depression and sleep disturbance and their effect on heart function.

Anxiety and depression as chronic and fluctuating events have an effect on all aspects of life. On the other hand, depression leads to a poor quality of life, worse functional status, and increased mortality (35). In addition, some studies have confirmed the positive effect of melatonin on depression symptoms and treatment of anxiety (36), sleep and circadian disturbances (37) especially among patients with acute coronary syndrome (38). In the present study, about half of the participants had severe depression symptoms and most of them had CADs. However, several studies have revealed that anxiety and depression increase the risk of CAD for healthy people (39-41), and depression symptoms among patients with CAD are

highly frequent (35,42), which is consistent with the findings of this study. The important point is the effect of depression on the severity of CAD, which has been confirmed by other studies (43-45).

Limitations

The main limitation of this study was determination of sleep quality for all participants. Sleep disturbance is one part of the PSQI which evaluates the sleep quality. Due to the effects of sleep disturbance on plasma concentration of melatonin, only the second part of the questionnaire (sleep disturbance) was completed.

Conclusion

A set of related factors influence the occurrence and severity of CAD. Melatonin as a protective factor affects the occurrence and severity of CAD, but the presence of some diseases like mental disorders can lead to a decrease in the plasma concentration of melatonin. As depression symptoms are frequent among patients with CAD and these patients have lower plasma concentration of melatonin, by treating depression and improving the melatonin synthesis and secretion cycle, the occurrence and severity of CAD may decrease.

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