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Association between Melatonin Value and Interleukins-1B, -18, and -33 Levels in Patients with Different Stages of Non-Alcoholic Fatty Liver Disease

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ABSTRACT

BACKGROUND:
Interaction between immune modulators and inflammatory factors is considered as one of the main underlying pathologies of non-alcoholic fatty liver disease (NAFLD). Hence we aimed to assess the association between these cytokines and melatonin.

METHODS:
We enrolled adult patients diagnosed with fatty liver by ultrasonography in a cross-sectional study. All of them underwent Fibroscan evaluation. The subjects who met the inclusion and exclusion criteria for NAFLD were involved. A normal group who did not have NAFLD, viral or non-viral hepatitis, and without a history of pancreatobiliary surgery, bariatric surgery, and intake of any medication that influence the liver was also selected. The participants were categorized into the three following groups: 1) fibrosis > 9.1 kPa and steatosis > 290 dbm, 2) fibrosis: 6-9.0 kPa and steatosis 240-290 dbm, and 3) normal group with fibrosis < 6.0 kPa and steatosis < 240 dbm. Laboratory assessment and a questionnaire including demographic, anthropometric, laboratories, and clinical data were completed for each of them.

RESULTS:
Totally 97 subjects were enrolled in the present study. The mean age of the subjects was 42.2 ± 11.3 years. 60% of them (59 patients) were female. Serum levels of melatonin, interleukin (IL)-1B, IL-18, and IL-33 increased according to the advancing of NAFLD state. Based on multiple linear regression model, melatonin was significantly associated with IL-1B (β = 2.8, $P < 0.001$, 95% CI = 1.41-4.19), IL-18 (β = 0.018, $P = 0.0005$, 95% CI = 0.006-0.03), and IL-33 (β = 0.31, $P = 0.045$, 95% CI = 0.008-0.62) after adjustment for other variables.

CONCLUSION:
Melatonin level has a strong association with these cytokines. This linkage probably influences on the development and progression of NAFLD. Therefore it can be hypothesized that the therapeutic approach that affects this process may have a significant impact.

KEYWORDS:
Melatonin; Cytokines; Interleukin; Non-alcoholic fatty liver disease; Liver fibrosis

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) become one of the most common chronic liver diseases worldwide. Its incidence may associate with the increasing prevalence of obesity and metabolic syndrome as well as their co-morbidities or even mortality.[1,2]

Despite its prevalence and worldwide studies, the underlying mechanisms of NAFLD development and progression have not fully elucidated. In this context different pathogenesis factors such as life style and diet, insulin resistance, intestinal dysbiosis, lipotoxicity, and hepatic inflammation have been proposed. Furthermore, cytokines and chemokine are involved in NAFLD pathogenesis. NAFLD include a wide spectrum of conditions from simple steatosis to NASH and cirrhosis, whether these conditions are associated as progression a disease or need to be considered separately needs more studies. In this context the inflammation's pathways have been attracted a lot of attention.[2,3] It is recognized that initiating the inflammatory process and producing inflammatory cytokines such as IL-1 and IL-18 as members of the IL-1 cytokine family play an essential role in disease advancement.[3,4] Moreover, innate immune system response to pathogens signals contribute to liver disease via pathogen-associated molecular patterns (PAMPs) and also endogenous alarm signals known as damage-associated molecular patterns (DAMPs).[4,5] Furthermore, neutrophil-derived substances may play a role in activating pro-inflammatory factors that consequently cause the activation of cytokines such as IL-1β, IL-18, and IL-33 that have considerable effects on NAFLD.[5-7] Therefore the activation or deactivation of these cytokines seems to be the crucial point in developing NAFLD.

Melatonin is a crucial multitasking molecule that is one of the primary immune modulators in humans.[8] Melatonin influences both pro-and anti-inflammatory cytokines, reducing chronic and acute inflammation. Undoubtedly the stability balance between pro-inflammatory and anti-inflammatory reactions has a clinical impact where melatonin works.[9-11] Melatonin also has a different clinical impact on different diseases such as sleep disorders and NAFLD.[12-14] Altogether interaction of melatonin with cytokines is an interesting topic that needs more assessment. Furthermore, there are not enough studies among patients with NAFLD, particularly with fatty liver and fibrosis states. In the present study, because of the critical role of these cytokines, from the IL-1 family, in developing NAFLD and also immunomodulatory effects of melatonin, we aimed to investigate the association between melatonin and these cytokines based on NAFLD state.

MATERIALS AND METHODS

The study population

In this cross-section study, we enrolled the patients referred to us between June 2017 and January 2019 who had been diagnosed with fatty liver. A group of normal subjects was also enrolled. The inclusion criteria were: adults aged more than 20 years and the presence of liver steatosis in transabdominal ultrasonography.

Exclusion criteria were viral hepatitis, autoimmune hepatitis, hepatic metabolic diseases, post-treatment of HCV infection, diabetes mellitus, bariatric surgery, taking medications with effects on liver status such as silymarin or oral antidiabetes; also an alcohol consumption of more than 30g/day in men and more than 20 g/day in women. 5 mL of fasting venous blood was taken from each patient for laboratory assessment and a questionnaire including demographic and anthropometric data was filled.

Ultrasonography

Fatty liver was defined on ultrasonography as normal, mild, moderate, and severe steatosis. The normal liver was defined when the consistency was homogeneous, displayed fine level echoes, minimally hyperechoic, or even isoechoic in contrast to the regular renal cortex.[15]

Liver transient elastography

Transient elastography was performed for detecting liver fibrosis by using Fibroscan (FibroScan; Echosens, Paris, France). The examination was performed according to the standard protocol, with the patient lying in dorsal decubitus with maximum abduction of the right arm. For each patient, at least 10 successful shots were considered as a correct exam. The results of fibrosis were reported in kilopascals (kPa). All patients underwent a Fibroscan (502 touch, Echosence Paris) assessment. All of the Fibroscan assessments were performed by a single expert physician.

According to the Fibroscan results, three groups of participants were defined: 1- normal subjects with normal

serum liver enzymes levels along with normal fibrosis (<5.8 kPa) and steatosis (<240 dbm); 2- Mild to moderate fibrosis, defined as fibrosis between 6-9.0 kPa, steatosis less than 290 dbm, and 3- the patients with severe fibrosis and suspect of steatohepatitis (NASH) as elevated liver enzymes, severe steatosis (>290 dbm) and fibrosis more than 9.1 kPa.[16,17]

Laboratory Methods

All patients' blood samples were assessed in the central lab of the hospital. The plasma and peripheral blood mononuclear cells (PBMC) and Buffy Coat were separated by using Phosphate Buffered Saline (PBS) as a buffer, and eventually, by adding ficoll, the PBMC was isolated. The three cytokines' levels were measured by ELISA kits (QuiagenGermani)

Data analysis

The descriptive data are presented as frequencies, percentages, and mean±SD. The univariate linear regression model was used to investigate the association between dependent variables (IL-1, IL-18, and IL-33) with melatonin and other variables. Multiple linear regression model was used to assess the independent effect of melatonin on cytokines. $P<0.05$ in analyses were considered statistically significant. The data were analyzed by STATA software version 15 (Stata Corp, Collage Station, TX, USA).

Ethics

This study was approved by the Ethics Committee of Iran University of Medical Sciences according to Helsinki declaration with the code IR.IUMS1397.32992. Written informed consent was obtained from each participant before enrollment.

RESULTS

Totally 97 subjects were enrolled in the present study. Table 1 illustrates the basic characteristics of the study population based on the different stages of fibrosis and steatosis.

The mean age of the study subjects was 42.2±11.3 years. 60% of them (59 patients) were female. As shown in table 1, the serum levels of melatonin, IL-1B, IL-18, and IL-33 increased according to the advancing of NAFLD phases.

In univariate analysis, we observed that variables such as age, triglyceride(TG), Aspartate transaminase(AST); Alanine aminotransferase (ALT); stage of fibrosis, stage of steatosis, and melatonin (tables 2-4) were associated with IL-1B, IL-18, and IL-33 ($P<0.05$).

In multiple analysis, melatonin was significantly associated with IL-1B ($\beta=2.8$, $P<0.001$), IL-18 ($\beta=0.018$, $P=0.0005$), and IL-33 ($\beta=0.31$, $P=0.045$) after adjustment for other variables (table 5).

DISCUSSION

In the present study, we illustrated that the values of cytokines IL-1B, IL18, and IL-33 had a strong association with melatonin levels in patients with NAFLD. By the way, the levels of cytokines and melatonin increased by advancing fibrosis and steatosis, most likely due to the underlying inflammatory pathways. Hence it may be suggested that melatonin is an immune modulator that influence on inflammatory process to balance the inflammation and anti-inflammation routes and eventually protect the cell injuries in NAFLD.

Despite many attempts to illustrate the underlying mechanism of developing and progression of NAFLD, the main pathogenesis pathways have not been well understood.[18,19] According to multiple hit theories along with known causes of fatty liver including insulin resistance and the accumulation of TG in the liver, other factors such as the inflammatory pathways and elements can be involved in developing and progressing of NAFLD.

Cytokines related to IL-1 have been recently considered in this regard.[6,7] However, the association between these cytokines and melatonin has not been well studied. In the present assessment, the increase the liver enzymes along with cytokines may reflect the underlying inflammatory process. Melatonin has an inhibitory effect on liver enzymes as well as the regulatory effect on cytokines imbalances.[20,21] Previous studies indicated that melatonin inhibits IL-1 and IL-18 in different situations such as sepsis.[22] Li zheng and colleagues and Chu j and co-workers demonstrated that melatonin played an important role in the neural system and could work as an antagonist on the inhibitory effect of IL-18 on neural stem cells proliferation.[23,24] In the liver, it is anticipated that an imbalance between inflammatory and anti-inflammatory

Table 1: Demographic and laboratory findings of study population according to different stages of fatty liver disease

Variable	Normal (N=42)	Mild to moderate (N=28)	Severe (N=27)	Total (N=97)	*P* value
Age (year)	36.5±10.1	45.1±11.4	47.4±10.0	42.2±11.3	<0.001
Sex					
Female	23	23	13	59	0.02
Male	19	5	14	38	
BMI					
<25	23	4	1	28	<0.001
≥25	19	24	26	69	
Total cholesterol (mg/dL)	169.0±45.3	210.4±64.1	205.4±36.1	189.6±52.2	0.02
LDL (mg/dL)	114.7±31.2	130.0±42.3	120.1±25.2	120.2±33.5	0.24
HDL (mg/dL)	44.2±9.3	44.8±9.4	41.9±7.7	43.8±8.9	0.55
Triglyceride (mg/dL)	124.1±60.0	189.4±97.2	197.0±103.4	161.1±89.8	0.001
AST (U/L)	21.4±7.3	53.6±37.7	57.4±30.7	40.7±31.1	<0.001
ALT (U/L)	21.0±10.7	66.1±46.2	74.0±40.7	48.8±41.3	<0.001
ALP (U/L)	159.9±53.8	215.5±64.2	221.9±45.6	193.2±61.8	<0.001
FBS	92.8±10.8	110.3±23.9	137.7±57.7	107.9±34.9	<0.001
Melatonin	332.4±459.8	494.4±507.0	610.3±508.0	457.1±496.1	0.07
IL-1B	1366.5±2367.63	1740.5±2155.78	3049.67±3076.46	1642.97±2601.21	0.002
IL-18	13.80±16.70	26.71±22.70	29.15±24.70	25.2±20.6	<0.00
IL-33	490.19± 416.68	767.88± 479.54	785.75± 488.47	624±447.3	0.001

BMI: body mass index; AST: Aspartate transaminase; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; FBS: Fasting blood sugar

Table 2: Univariate analyses of melatonin association with IL-1B

Variables	Coefficient	Std. Err	t	*P* value	95% CI
Sex (Female)	-326	572.87	-0.60	0.50	-1403.73, 751.72
Age	21.47	23.81	0.90	0.37	-25.83, 68.78
BMI	6.50	7.22	0.90	0.30	-7.85, 20.84
Total cholesterol (mg/dL)	1.30	5.64	0.24	0.81	-9.89, 12.55
LDL (mg/dL)	-1.73	9.14	-0.20	0.85	-19.90, 16.48
HDL (mg/dL)	32.03	34.04	0.94	0.35	-35.74, 99.80
Triglyceride (mg/dL)	2.48	3.32	0.75	0.45	-4.12, 9.10
AST (U/L)	24.59	8.20	3.00	0.003	8.31, 40.86
ALT (U/L)	21.52	6.03	3.54	0.001	9.45, 33.59
Alkaline phosphatase (U/L)	5.32	4.28	1.24	0.20	-3.17, 13.83
FBS	16.42	8.90	1.85	0.060	-1.30, 34.17
Stages of fibrosis					
Mild to moderate	374	617.10	0.61	0.05	-851.28, 1599.28
Severe	1683.17	623.90	2.70	0.006	444.35, 2921.99
Stages of steatosis					
Mild to moderate	-20.58	721.72	-0.03	0.977	-1453.59, 1412.43
Severe	1472.96	594.78	2.48	0.015	292.01, 2653.91
Melatonin	3.45	0.40	8.53	<0.001	2.64, 4.25

BMI: body mass index; AST: Aspartate transaminase; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; FBS: Fasting blood sugar

Table 3: Univariate analyses of melatonin association with IL-18

Variables	Coefficient	Std. Err	t	*P* value	95% CI
Sex (Female)	7.07	4.53	1.56	0.12	-1.90, 16.06
Age	0.38	0.192	2.0	0.04	0.00, 0.76
BMI	0.07	0.06	1.29	0.20	-0.04,0.20
Total cholesterol (mg/dL)	0.04	0.04	0.98	0.33	-0.04, 0.13
LDL (mg/dL)	-0.03	0.07	-0.46	0.63	-0.18,0.11
HDL(mg/dL)	0.11	0.27	0.40	0.60	-0.44, 0.66
Triglyceride(mg/dL)	0.05	0.02	2.15	0.03	0.00, 0.10
AST (U/L)	0.26	0.06	3.90	<0.001	0.13, 0.39
ALT (U/L)	0.18	0.05	3.64	<0.001	0.08, 0.28
ALP (U/L)	0.05	0.03	1.55	0.12	-0.01, 0.12
FBS	0.10	0.07	1.49	0.14	-0.03, 0.25
Stages of fibrosis					
Mild to moderate	14.61	5.14	2.84	0.006	4.38, 24.83
Severe	12.05	5.20	2.32	0.02	1.71, 22.40
Stages of steatosis					
Mild to moderate	2.46	6.14	0.40	0.689	-9.73, 14.65
Severe	12.13	5.06	2.40	0.018	2.09, 22.18
Melatonin	0.02	0.00	5.85	<0.001	0.01, 0.03

BMI:body mass index; AST: Aspartate transaminase; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; FBS: Fasting blood sugar

Table 4: Univariate analyses of melatonin association with IL-33

Variables	Coefficient	Std. Err	t	*P* value	95% CI
Sex (Female)	25.75	98.91	0.29	0.70	-167.62, 225.12
Age	7.80	4.23	1.85	0.06	-0.59, 16.24
BMI	2.05	1.32	1.55	0.12	-0.58,4.70
Total cholesterol (mg/dL)	0.44	1.00	0.42	0.70	-1.60, 2.42
LDL (mg/dL)	-0.07	1.60	-0.05	0.90	-3.27, 3.12
HDL (mg/dL)	-4.80	5.90	-0.80	0.42	-16.72, 7.11
Triglyceride (mg/dL)	0.86	0.60	1.50	0.13	-0.27, 2.02
AST (U/L)	2.42	1.15	2.11	0.03	0.14, 4.70
ALT (U/L)	2.90	1.53	1.90	0.04	-0.10,6.00
ALP (U/L)	1.52	0.80	1.97	0.05	-0.02, 3.05
FBS	2.36	1.60	1.50	0.14	-0.83, 5.56
Stages of fibrosis					
Mild to moderate	295.55	111.23	2.60	0.001	74.70,516.42
Severe	277.70	112.50	2.50	0.01	54.39,501.00
Stages of steatosis					
Mild to moderate	30.38	134.68	0.23	0.822	-237.03, 297.79
Severe	185.72	110.99	1.67	0.098	-34.66, 406.09
Melatonin	0.42	0.90	4.75	<0.001	0.25, 0.60

BMI: body mass index; AST: Aspartate transaminase; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; FBS: Fasting blood sugar

Table 5: Multiple analyses of melatonin association with cytokines

Variables	Coefficient	Std. Err	t	*P* value	95% CI
IL-1B	2.80	0.69	4.06	<0.001	1.41, 4.19
IL-18	0.018	0.006	2.99	0.005	0.006, 0.03
IL-33	0.31	0.15	2.07	0.045	0.008, 0.62

factors are present. Indeed, melatonin were used as treatment of NAFLD, previous reports illustrated that melatonin therapy decreased the severity of steatosis, inhibited the immigration of inflammatory cells, protected hepatic cells from damage, and also reduced serum and tissue inflammatory cytokines concentration.[25-27]

We also revealed the increasing level of IL-1β and IL-18 by advancing the fibrosis. This association may be reflected in the role of these cytokines in NAFLD. By the way, melatonin is located in a position that affects on different pathways. Melatonin can reduce inflammation and liver injury by inhibiting pro-inflammatory cytokine production. The question that comes to mind is that despite the increase of melatonin, why did we observe the increasing levels of cytokines? We cannot offer an exact response. It could be due to the protective ability of melatonin. In NAFLD, melatonin may present its inhibitory effect on inflammation reactions in higher doses, or the ability or effective melatonin concentration is not enough. Also, melatonin can be a part of the immune response. Moreover, other pathways involved in NAFLD development that work together or individuals should be considered. All of these hypotheses need more studies.

By advancing of the stages of fibrosis among our participants we observed an increasing trend of IL-1 as well as IL-18 levels. The role of IL-1 in liver diseases has been investigated. In NAFLD, IL-1 stimulates liver steatosis, inflammation, and fibrosis.[28] Negrin KA and others [29] reported that IL-1 acts as a trigger of hepatic steatosis development. Also, it was illustrated that IL-1B concentration increased in obese patients and in insulin resistance state and decreased after weight loss.[30,31] Furthermore, IL-1B may involve initiating local immune cells reactions and leucocytes infiltration to the liver that eventually leads to a chronic inflammatory state [32,33] Regarding IL-18, it is demonstrated that the plasma concentration of IL-18 in patients with metabolic syndrome is associated with the development of insulin resistance and atherosclerosis.[34] High plasma concentrations of IL-18 promote inflammation and metabolic disturbances, or whether the increased concentrations reflect a compensatory mechanism needs more studies in the future. Consistent with our results, previous studies demonstrated elevated circulating levels of IL-18 in adult patients with metabolic syndrome.[35,36] Flisiak-Jackiewicz M and colleagues demonstrated that IL-18 in obese children significantly increased among NAFLD compared with the control subjects. They revealed that serum IL-18 level correlated with hepatocyte injury, systemic inflammation, and degree of liver steatosis. The results support the role of IL-18 in the development of NAFLD.[37]

IL-33 has been proven as a pathogenic marker in patients with liver cirrhosis, liver failure, and liver fibrosis.[33,38] Administration of IL-33 intraperitoneally in an animal model of diet-induced liver steatosis worsened the liver fibrosis by inducing invading macrophages and T cells that provoke pro-fibrotic cytokines such as IL-13.[39] In this context, it was shown that IL-33 significantly increased in patients with liver fibrosis compared with the control group.[40] It is revealed that recombinant IL-33 aggravated hepatic fibrosis in induced steatohepatitis.[41,42] By the way, as proposed earlier, melatonin has an anti-inflammatory effect on the liver, along with that melatonin and IL-33 have interactions.[43,44] Onk d. and colleagues in a study on oxidative stress revealed the inhibitory effect of melatonin on IL-33.[43] Here we observed the elevation of both substances together. The exact explanation is unclear, but our former hypothesis may be indicated.

Our study had some limitations as the number of participants was limited. Also, we need to consider the circadian rhythm for melatonin levels.

In conclusion, despite the widespread incidence of NAFLD, the main mechanism of its development and progression is not understood well. IL-1B, IL-18, and IL33 have serious influences in this regard. Melatonin can interact with this pathway and regulate the cytokine imbalance for NAFLD improvement and treatment. This effect is not associated with lipid and FBS concentration as well as liver enzymes. Moreover, we should consider the circadian rhythms and their effects on melatonin and mast cells and their dependent immune reactions.

ETHICAL APPROVAL

There is nothing to be declared.

CONFLICT OF INTEREST

The authors declare no conflict of interest related to this work.

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