J Surg Med. 2019;3(1):22-26.
DOI: 10.28982/josam.443902

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN: 2602-2079

Melatonin, leptin, and ghrelin levels in nurses working night shifts

Gece vardiyasında çalışan hemşirelerde melatonin, leptin ve grelin düzeyleri

Sibel Söylemez [1], Ayşe Banu Çaycı Sivri [1], Ercan Şimşek [1], Burçak Polat [2], Bekir Çakır [2]

[1] Department of Biochemistry, School of Medicine, Gazi University, Ankara, Turkey
[2] Department of Clinic of Endocrinology and Metabolism, Atatürk Training and Research Hospital, Ankara, Turkey

ORCID ID of the authors:
SS: 0000-0002-5005-2277
ABÇS: 0000-0003-1379-5159
EŞ: 0000-0002 -9010-6196
BP: 0000-0002-7729-5586
BÇ: 0000-0001-7526-8827

Corresponding author / Sorumlu yazar:
Sibel Söylemez
Address / Adres: Gazi Üniversitesi Tıp Fakültesi, Biyokimya Anabilim Dalı, Ankara, Türkiye
E-mail: soylemezsibel@gmail.com

Ethics Committee Approval: Gazi University, Clinical Research Ethics Committee, 09.06.2014/306.
Etik Kurul Onayı: Gazi Üniversitesi Klinik Araştırmalar Etik Kurulu, 09.06.2014/306.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: This study was supported by a research grant from Gazi University Scientific Research Projects Unit (01/2014-27, 30.12.2014).
Finansal Destek: Bu çalışma Gazi Üniversitesi Bilimsel Araştırmalar Birimi tarafından finansal olarak desteklenmiştir. (01/2014-27, 30.12.2014).

Previous presentation: This work was previously presented as oral presentation at the International Biochemical Congress 2017- 28th National Biochemistry Congress 19-23 September 2017, Erzurum, Turkey.

Received / Geliş Tarihi: 14.07.2018
Accepted / Kabul Tarihi: 23.08.2018
Published / Yayın Tarihi: 10.09.2018

Abstract

Aim: The levels of several hormones including melatonin, leptin, and ghrelin are regulated by circadian rhythm. Deregulated hormone levels due to disruption of circadian rhythm may result in medical conditions like metabolic syndrome (MetS). The aim of this cross-sectional study was to investigate the associations among circadian rhythm, melatonin, leptin, ghrelin and metabolic syndrome by determining melatonin levels of healthy nurses who were working on night-shift for at least 3 months and of those on day-shift for at least 3 months.

Methods: Venous bloods following 8-hour fasting of 50 nurses, who were aged at 20-40 age range and whose Body Mass Index (BMI) were >25, were collected. Those working on night-shift were named as night group and the control group of the study was named as day group. From the bloods collected; melatonin, leptin and ghrelin levels were evaluated by ELISA method, insulin was evaluated by immunochemically, whereas fasting blood glucose, cholesterol, triglyceride, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) levels were evaluated spectrophotometrically.

Results: Melatonin level was significantly lower in the night-shift group compared to the day-shift group (p=0.003). Leptin level was slightly but not significantly lower in the night-shift group (p=0.097). In contrast, ghrelin level and other biochemical parameters including triglyceride, fasting blood sugar (FBS), insulin, insulin resistance index (HOMA-IR) and cholesterol were increased in the night-shift group but these increments were not statistically significant.

Conclusion: Our results suggest that night-shift work might exhibit tendency towards MetS by disrupting circadian rhythm.

Keywords: Night shift, Metabolic syndrome, Melatonin, Leptin, Ghrelin

Öz

Amaç: Melatonin, leptin ve grelin dahil olmak üzere birçok hormonun seviyeleri sirkadiyen ritim tarafından düzenlenir. Sirkadiyen ritim bozulmasına bağlı düzensiz hormon düzeyleri metabolik sendrom (MetS) gibi sorunlara neden olabilir. Bu kesitsel çalışmada, en az 3 aydır gece ve en az 3 aydır gündüz vardiyasında çalışan sağlıklı hemşirelerin melatonin düzeylerini belirleyerek, melatonin, sirkadien ritim, leptin, grelin ve metabolik sendrom ilişkisinin araştırılması amaçlanmıştır.

Yöntemler: 20-40 yaş aralığında, Vücut Kitle İndeksi (BMI) > 25 olan 50 hemşirenin sabah 8 saatlik açlıkla venöz kanları alınmıştır. Gece nöbet tutan grup gece grubu olarak, gündüz çalışan kontrol grubu ise gündüz grubu olarak adlandırılmıştır. Alınan kanlarda melatonin, leptin ve grelin düzeyleri ELISA metodu ile, metabolik sendrom kriterlerinden olan insülin immünokimyasal olarak, açlık kan şekeri, kolesterol, trigliserid, yüksek yoğunluklu lipoprotein (HDL) ve düşük yoğunluklu lipoprotein (LDL) düzeyleri ise spektrofotometrik olarak incelenmiştir.

Bulgular: Melatonin düzeyleri gece grubunda, gündüz grubuna göre anlamlı derecede düşük bulunmuştur (p=0,003). Leptin düzeyleri gece grubunda düşük bulunmuştur ancak istatistiksel olarak anlamlı değildir (p=0,097). Aksine grelin düzeyleri ve diğer biyokimyasal parametreler olan trigliserit, açlık kan şekeri, insülin, insülin direnci ve kolesterol gece grubunda artmıştır, ancak bu artışlar istatistiksel olarak anlamlı değildir.

Sonuç: Bulgularımız gece vardiyasında çalışmanın sırkadiyen ritmin bozularak, MetS eğiliminin artabileceğini göstermektedir.

Anahtar kelimeler: Gece vardiyası, Metabolik sendrom, Melatonin, Leptin, Grelin

Introduction

Working night shift has deleterious effects on health by disrupting human body circadian rhythm. It was considered to be a risk factor for obesity and a wide range of chronic diseases and chronic medical conditions. Approximately 2-5% of workers have disorders associated with working night shifts [1,2]. The levels of several hormones including melatonin, leptin and ghrelin are regulated by circadian rhythm. Any deterioration in circadian rhythmicity may result in medical conditions like metabolic syndrome by changing hormone levels [3].

Melatonin, characterized at 1958 by Lerner et al., is secreted at night under dark condition and involved in the phasing of circadian rhythm. The circadian rhythm regulates physiological processes including immune system, antioxidant defenses, glucose regulation, and the control of sleep through melatonin signal [4,5].

The metabolic syndrome (MetS) lowers quality of life by increasing the risk of a range of disorders including type 2 diabetes mellitus (T2DM), cardiovascular disease (CVD), and polycystic over syndrome (PCOS). A cluster of metabolic abnormalities including insulin resistance, abdominal (visceral) obesity, genetic susceptibility, high serum triglycerides, low high-density lipoprotein (HDL) levels, atherogenic dyslipidemia, elevated blood pressure, and chronic stress have been considered as components of MetS [6]. The prevalence of MetS was estimated to range from 20% to 30% in most countries and increases continuously. MetS is considered to be the most serious health problem for 21st century. The increased incidence of obesity in populations may be a major reason for the elevated prevalence of MetS worldwide [7].

Although the etiopathogenesis is still unclear, obesity lead to MetS by disrupting metabolic parameters including insulin resistance, blood pressure, cholesterol, and triglycerides [8]. Adipose tissue as an endocrine organ is involved in whole body homeostasis by secreting adipokines (adipocytokines) [9]. Leptin was characterized by Zhang et al. in 1994 as the first adipokine [10]. The primary function of leptin is to prevent the formation of obesity by regulating food intake of organism. While serum leptin level decreases in case of fasting and after weight loss, leptin production increases in obesity. The elevated level of leptin induce low grade inflammation, and affects cytokine production [11]. Ghrelin, another adipokine, was characterized by Kojima et al. in 1999 [12]. Ghrelin is mainly secreted by stomach to regulate food intake. In contrast to leptin, ghrelin secretion increases in starvation in a fast-acting manner. In addition, the involvement of ghrelin in the regulation of immunity and inflammation has been established in detail [13].

The aim of this study is to investigate the potential contribution of night-shift work on the development of metabolic syndrome. To this and, peripheral blood samples were taken from nurses working day-shifts and night-shifts, and the levels of melatonin, leptin and ghrelin were analyzed.

Materials and methods

Study participants

The study population comprised 50 female nurses working at a research hospital. The subjects were aged between 20 and 40 years in premenopausal period. They were healthy non-smoker individuals had no any medical treatment or no metabolic diseases such as thyroid, diabetes mellitus, hyperlipidemia, or hypertension. The night-shift group (NSG) consisted of 25 subjects that were required to work night shift for at least 3 months. The day-shift group (DSG) consisted of 25 subjects that were required to work day shift for at least 3 months. The physical (weight and height) and biochemical data were obtained for all subjects. The study protocol was approved by Institutional Ethics Committee. The study was carried out according to Declaration of Helsinki. All subjects gave written informed consent before participation.

Blood Sampling

A venous blood sample of 10 mL was drawn from all subjects at 8 o'clock in the morning after 8 hours of fasting and stored in pre-cooled biochemical tubes. In the NSG, the blood samples were obtained at the end of the night shift. In the DSG, the blood samples were obtained at the beginning of the day shift. Within 15 minutes of sample collection, the blood sample was spun at 1800 g for 10 min using a refrigerated centrifuge (4°C), and incubated for some time for phase separation. Then, the supernatant was transferred into polypropylene tubes and stored at –80 °C for analysis of relevant hormones or biochemical parameters.

Biochemical parameters

Plasma melatonin, leptin, and ghrelin concentrations were determined by enzyme-linked immunosorbent assay (ELISA) method. For this, commercially available melatonin (Catalogue Number: E-EL-H2016, Elabscience, Wuhan, China), leptin (Catalogue Number: KAP2281, DIAsource, Nivelles, Belgium), and ghrelin (Catalogue Number: E-EL-H1919, Elabscience, Wuhan, China) ELISA kits were used according to manufacturers' instructions.

Other relevant laboratory parameters including high and low density lipoprotein (HDL and LDL), fasting blood sugar (FBS), insulin, cholesterol, and serum triglyceride were determined on Cobas ® 8000 modular analyzer (Roche Diagnostics, Basel, Switzerland) via photometric and immunochemical methods.

Calculation of body mass index and insulin resistance index

Body mass index was calculated as the body mass divided by the square of the body height (kg/m2) for all participants. Insulin resistance index was calculated by using formula of homeostasis model assessment (HOMA-IR) method:

HOMA-IR = Fasting insulin (μU/mL) x Fasting glucose (mg/dL) / 405

Statistical analysis

Statistical analyses were performed using Predictive Analytics Software (PASW) statistical software (version 15.0 for Windows; SPSS Inc., Chicago, Illinois). Descriptive parameters were presented as median. Since the number of data is below 30, parametric conditions were not provided, and then nonparametric tests were used to analyses. For comparison of independent variables in the two groups, Mann-Whitney U tests were used. Correlation analysis was also performed with the nonparametric test, Spearman correlation. A p value less than 0.05 were accepted as statistically significant.

Results

The characteristics and laboratory parameters of the DSG and NSG were summarized in Table 1. Body mass indices (BMI) of all subjects were more than 25 kg/m2. No significant difference was found between the BMI values of the NSG (26.81, 25.71 - 32.05) and DSG (27.89, 26.99 - 29.69). Melatonin level was significantly lower in the NSG (p=0.003). Leptin level was also lower in the NSG but the difference was not statistically significant (p=0.097). Likewise, ghrelin level and other biochemical parameters including triglyceride, FBS, insulin, HOMA-IR, and cholesterol were found higher in the NSG albeit not statistically significant (p=0.308, p=0.356, p=0.915, p=0.923, p=0.884, respectively).

Correlation analyses for parameters of the DSG and NSG were done by Spearman's rho test. Strong positive correlation was found between HDL and melatonin levels (r: 0.602, p=0.001) in the NSG. In contrast, weak negative correlations were found between melatonin and insulin levels (r: -0.427, p=0.033) and between melatonin level and HOMA-IR (r: -0.420, p=0.036) in the DSG. A weak negative correlation was also observed between insulin and leptin levels in the NSG (r: -0.425, p=0.034).

Table 1: Comparison of characteristics and laboratory parameters in the day-shift and night-shift groups

Variables	Day-shift group Mean (Min.-Max.)	Night-shift group Mean (Min.-Max.)	p*
Melatonin (pg/mL)	534.11(295.39-657.54)	273.98 (202.33 - 390.29)	0.003
Leptin (ng/mL)	4.88 (2.8 - 7.31)	3.95 (1.64 - 5.8)	0.097
Ghrelin (ng/mL)	1.57 (1.08 - 3.43)	2.03 (0.9 - 4.36)	0.977
FBS (mg/dL)	86 (84 - 91)	88 (82 - 94)	0.356
Insulin (μU/mL)	8.83 (6.87 - 12.43)	10.1 (6.51 - 13.2)	0.915
HOMA-IR	2 (1.32 - 2.81)	2 (1.59 - 2.77)	0.923
Cholesterol (mg/dL)	182 (173 - 205)	193 (166 - 237)	0.884
Triglyceride (mg/dL)	88 (68 - 130)	109 (86 - 154)	0.308
HDL (mg/dL)	48 (43 - 53)	47 (37 - 58)	0.892
LDL (mg/dL)	101 (90 - 115)	117 (95 - 145)	0.084
BMI (kg/m^2)	27.89 (26.99 - 29.69)	26.81 (25.71 - 32.05)	0.985

*Mann-Whitney U test, FBS: Fasting Blood Sugar, HOMA-IR: Homeostatic Model Assessment-Insulin Resistance, HDL: High Density Lipoprotein, LDL: Low Density Lipoprotein, BMI: Body Mass Index

Discussion

The metabolic syndrome (MetS) involves several metabolic abnormalities, and creates risks for wide range of disorders. Increased prevalence of MetS is a problem in developed and developing countries. Night-shift work is a reality in industrialized populations, and nearly 15% of all employees were estimated to work at nights regularly, including nurses. The effect of working style and condition on the health of nurses has been shown before [14,15]. It was established that the night-shift work makes strong tendency towards the development of MetS by disrupting circadian rhythm, but underlying mechanisms has not been elucidated yet [16]. For this; plasma melatonin, leptin, ghrelin and other relevant biochemical parameters were comparatively investigated in nurses' working day and night-shifts. These hormones were accepted as immune system regulators and the levels of them were regulated by circadian rhythm [3,17]. Our study found a significantly decreased level of plasma melatonin in the NSG. In addition, the HOMA-IR and the plasma levels of ghrelin, triglyceride, FBS, insulin, and cholesterol were increased in the NSG albeit not statistically significant (Table 1). This suggests that night-shift work is a risk factor for the MetS.

Several metabolic processes in human body, such as hormone secretion, are regulated by circadian rhythm. Although circadian rhythm is generated endogenously, it can be modulated by external factors such as the sunlight exposure and redox cycle. The most likely external factor to disrupt circadian rhythm is the contamination of night with light. The peak level of melatonin is reached under dark condition in the middle of night. The employees working at night shift are exposed to artificial light leading to melatonin deficiency in the body [5,18]. Similar to our findings, several studies found decreased levels of melatonin and urinary 6-sulfatoxymelatonin (the primary metabolite of melatonin) in night-shift workers [19]. Suppressed levels of melatonin may lead to MetS as well as cancers although the level of melatonin in response to light exposure during night varies depending on racial differences [20]. The primary mechanism in prevention of MetS by melatonin is considered to be through the antioxidant effect of melatonin. The roles of the oxidative stress in the development of MetS and the anti-oxidant effect of melatonin by direct radical scavenging or upregulating several antioxidant enzymes have been demonstrated before [5, 21]. Ulas et al. [15] have previously shown the increased levels of oxidative stress parameters in nurses working night shifts. Besides the lack of anti-oxidant effect, melatonin depletion is also associated with deterioration of various metabolic parameters such as increased triglyceride, FBS, insulin, HOMA-IR, and cholesterol levels in the MetS [22]. Although not statistically significant; triglyceride, FBS, insulin, HOMA-IR, and cholesterol levels were increased in the NSG compared with the DSG.

In a study of melatonin usage as a therapeutic agent, melatonin was given to animal models (rat, hamster) with MetS [23]. The study demonstrated a melatonin-induced protection against functional and metabolic impairment. In addition, a strong positive correlation between HDL and melatonin was found in that study, similar to the findings of the current study. The reduction in melatonin production has been linked to deficiency in insulin-signaling pathway and insulin resistance, and melatonin usage as a supplement has been recommended to protect against metabolic syndrome for the night-shift workers [24,25]. The weak negative correlations between the levels of melatonin and insulin and between the melatonin level and HOMA-IR in the DSG in our study support Cipolla Neto's proposal [25]. Solak et al. [26] previously established a relationship between leptin and insulin levels. Similarly, a weak negative correlation was observed between insulin and leptin level in the NSG in our study.

Obesity has already been defined as a risk factor for MetS [27]. It was proposed that short sleep duration and night-shift work lead to obesity [28,29]. Although, the mechanism between night-shift work and obesity has not been elucidated in detail, that the night-shift work induces more consumption of unhealthy food and associated with less energy expenditure were assumed to be main factors for obesity [30]. A recent study by Shea et al. revealed that a fluctuation in leptin level controlled by circadian rhythm may be responsible for obesity related to night-shift work [31]. Nowadays, the linkage between circadian rhythm and adipokines including leptin and ghrelin has been described [3]. Leptin and ghrelin are two main actors in energy

balance. The imbalance between them is the primary reason for obesity [32]. In our study, leptin level was decreased and ghrelin level was increased in night-shift workers albeit not significantly. These may cause more food intake by increasing appetite and thus lead to obesity in the long term. These results are in concordance with those of Taheri et al. [33] who used questionnaires, sleep diaries, and blood samples from 1024 individuals to investigate the effect of sleep duration on leptin, ghrelin, and BMI. They concluded that short or altering sleep duration elevated ghrelin levels and reduced leptin levels. This imbalance partially explained the increase in appetite after acute partial sleep deprivation [34]. Over-eating for a long period of time increases the circulating leptin levels to stop feeding. However, a sustained increase in leptin level disrupts the leptin system, and thus, hypothalamus develops a leptin resistance. This also explains why leptin level remains high in obese individuals compared with healthy individuals. Another factor accompanying the high leptin level is low-grade inflammation. Inflammation is another component of MetS, and leptin shows low-grade inflammation in contrast to melatonin [35,36]. So, obesity can make contribution to the development of MetS by formation of inflammation [37]. The metabolic syndrome is a multifactorial medical condition known as the black plague of the 21st century. Night-shift work was shown to be a risk factor for MetS formation [38]. Melatonin, leptin, and ghrelin are defined as immune system regulators and establish a linkage between metabolism and the immune system [17,39]. Melatonin-based therapeutic approaches have already been established [20,40]. However, underlying mechanisms has not been described in detail. The identification of these mechanisms and those at risk may be useful in the development of new treatment methods.

Limitations

An important limitation of our study was low sample size. This was in part due to the relatively strict exclusion criteria that we applied. We only enrolled the nurses who do not smoke, do not use any medication, have BMI>25, and do not have any metabolic disease, which narrowed down the population we can work with. Another important limitation was the enrollment of different nurses in the NSG and DSG. Studying the same group of nurses during a night-shift period and day-shift period was not possible since the nurses in this particular hospital have continuously worked day shift or night shift without switching between two shifts.

Conclusions

Our experimental data suggests that the reduction of melatonin level and impaired balance between leptin and ghrelin might contribute to the development of MetS. Melatonin system has already been targeted for therapeutic purposes; however, new therapeutic approaches targeting the melatonin, leptin, and ghrelin systems simultaneously might be developed for MetS. Further investigations are needed to describe how these agents may be used as targets in treatment of MetS.

References

1. Boivin DB, Boudreau P. Impacts of shift work on sleep and circadian rhythms. Pathol Biol (Paris). 2014;62(5):292-301.
2. Caruso CC. Negative impacts of shiftwork and long work hours. Rehabil Nurs. 2014;39(1):16-25.
3. Kim TW, Jeong JH, Hong SC. The impact of sleep and circadian disturbance on hormones and metabolism. Int J Endocrinol. 2015;2015:591729.
4. Claustrat B, Leston J. Melatonin: Physiological effects in humans. Neurochirurgie. 2015;61(2-3):77-84.
5. Hardeland R, Cardinali DP, Srinivasan V, Spence DW, Brown GM, Pandi-Perumal SR. Melatonin--a pleiotropic, orchestrating regulator molecule. Prog Neurobiol. 2011;93(3):350-84.
6. Kaur J. A comprehensive review on metabolic syndrome. Cardiol Res Pract. 2014;2014:943162.
7. Grundy SM. Metabolic syndrome pandemic. Arterioscler Thromb Vasc Biol. 2008;28(4):629-36.
8. Dominguez LJ, Barbagallo M. The biology of the metabolic syndrome and aging. Curr Opin Clin Nutr Metab Care. 2016;19(1):5-11.
9. Booth A, Magnuson A, Fouts J, Foster MT. Adipose tissue: an endocrine organ playing a role in metabolic regulation. Horm Mol Biol Clin Investig. 2016;26(1):25-42.
10. Zhang Y, Proenca R, Maffei M, Barone M, Leopold L, Friedman JM. Positional cloning of the mouse obese gene and its human homologue. Nature. 1994;372(6505):425-32.
11. Oswal A, Yeo G. Leptin and the control of body weight: a review of its diverse central targets, signaling mechanisms, and role in the pathogenesis of obesity. Obesity (Silver Spring) 2010;18(2):221-9.
12. Kojima M, Hosoda H, Date Y, Nakazato M, Matsuo H, Kangawa K. Ghrelin is a growth-hormone-releasing acylated peptide from stomach. Nature. 1999;402(6762):656-60.
13. Collden G, Tschop MH, Muller TD. Therapeutic Potential of Targeting the Ghrelin Pathway. Int J Mol Sci. 2017;18(4). doi: 10.3390/ijms18040798
14. Turker Y, Bas FY, Yavuz E, Arslan B. Knowledge, Attitude and Behavior of Midwives and Nurses Working Primary Health Services on Family Planning. Prusias Medical Journal. 2016;1(1):1-5.
15. Ulas T, Buyukhatipoglu H, Kirhan I, Dal MS, Eren MA, Hazar A, et al. The effect of day and night shifts on oxidative stress and anxiety symptoms of the nurses. Eur Rev Med Pharmacol Sci. 2012;16(5):594-9.
16. Pietroiusti A, Neri A, Somma G, Coppeta L, Iavicoli I, Bergamaschi A, et al. Incidence of metabolic syndrome among night-shift healthcare workers. Occup Environ Med. 2010;67(1):54-7.
17. Jaworek J, Konturek SJ. Hormonal protection in acute pancreatitis by ghrelin, leptin and melatonin. World J Gastroenterol. 2014;20(45):16902-12.
18. Reiter RJ, Tan DX, Erren TC, Fuentes-Broto L, Paredes SD. Light-mediated perturbations of circadian timing and cancer risk: a mechanistic analysis. Integr Cancer Ther. 2009;8(4):354-60.
19. Davis S, Mirick DK, Chen C, Stanczyk FZ. Night shift work and hormone levels in women. Cancer Epidemiol Biomarkers Prev. 2012;21(4):609-18.
20. Nduhirabandi F, du Toit EF, Lochner A. Melatonin and the metabolic syndrome: a tool for effective therapy in obesity-associated abnormalities? Acta Physiol (Oxf). 2012;205(2):209-23.
21. Konturek SJ, Konturek PC, Brzozowska I, Pawlik M, Sliwowski Z, Czesnikiewicz-Guzik M, et al. Localization and biological activities of melatonin in intact and diseased gastrointestinal tract (GIT). J Physiol Pharmacol. 2007;58(3):381-405.
22. Karlsson BH, Knutsson AK, Lindahl BO, Alfredsson LS. Metabolic disturbances in male workers with rotating three-shift work. Results of the WOLF study. Int Arch Occup Environ Health. 2003;76 (6):424-30.
23. Cardinali DP, Bernasconi PA, Reynoso R, Toso CF, Scacchi P. Melatonin may curtail the metabolic syndrome: studies on initial and fully established fructose-induced metabolic syndrome in rats. Int J Mol Sci. 2013;14(2):2502-14.
24. Sheu WH, Shieh SM, Fuh MM, Shen DD, Jeng CY, Chen YD, et al. Insulin resistance, glucose intolerance, and hyperinsulinemia. Hypertriglyceridemia versus hypercholesterolemia. Arterioscler Thromb. 1993;13(3):367-70.
25. Cipolla-Neto J, Amaral FG, Afeche SC, Tan DX, Reiter RJ. Melatonin, energy metabolism, and obesity: a review. J Pineal Res. 2014;56(4):371-81.
26. Solak A, Tuncel P. Leptin, Adiponectin, Oxidized LDL Levels and Paraoxonase Activity in Metabolic Syndrome. Journal of Turkish Clinical Biochemistry. 2009;7(1):23-9.
27. Kassi E, Pervanidou P, Kaltsas G, Chrousos G. Metabolic syndrome: definitions and controversies. BMC Med. 2011;9:48.

28. Itani O, Kaneita Y, Murata A, Yokoyama E, Ohida T. Association of onset of obesity with sleep duration and shift work among Japanese adults. Sleep Med. 2011;12(4):341-5.
29. Lasfargues G, Vol S, Caces E, Le Clesiau H, Lecomte P, Tichet J. Relations among night work, dietary habits, biological measure, and health status. Int J Behav Med. 1996;3(2):123-34.
30. Ha M, Park J. Shiftwork and metabolic risk factors of cardiovascular disease. J Occup Health. 2005;47(2):89-95.
31. Shea SA, Hilton MF, Orlova C, Ayers RT, Mantzoros CS. Independent circadian and sleep/wake regulation of adipokines and glucose in humans. J Clin Endocrinol Metab. 2005;90(5):2537-44.
32. Klok MD, Jakobsdottir S, Drent ML. The role of leptin and ghrelin in the regulation of food intake and body weight in humans: a review. Obes Rev. 2007;8(1):21-34.
33. Taheri S, Lin L, Austin D, Young T, Mignot E. Short sleep duration is associated with reduced leptin, elevated ghrelin, and increased body mass index. PLOS Med. 2004;1(3):e62.
34. Brondel L, Romer MA, Nougues PM, Touyarou P, Davenne D. Acute partial sleep deprivation increases food intake in healthy men. Am J Clin Nutr. 2010;91(6):1550-9.
35. Baker RG, Hayden MS, Ghosh S. NF-kappaB, inflammation, and metabolic disease. Cell Metab. 2011;13(1):11-22.
36. Cardinali DP, Hardeland R. Inflammaging, Metabolic Syndrome and Melatonin: A Call for Treatment Studies. Neuroendocrinology. 2017;104(4):382-97.
37. Engin A. The Pathogenesis of Obesity-Associated Adipose Tissue Inflammation. Adv Exp Med Biol. 2017;960:221-45.
38. De Bacquer D, Van Risseghem M, Clays E, Kittel F, De Backer G, Braeckman L. Rotating shift work and the metabolic syndrome: a prospective study. Int J Epidemiol. 2009;38(3):848-54.
39. Perez-Perez A, Vilarino-Garcia T, Fernandez-Riejos P, Martin-Gonzalez J, Segura-Egea JJ, Sanchez-Margalet V. Role of leptin as a link between metabolism and the immune system. Cytokine and Growth Factor Rev. 2017;(35):71-84.
40. Kozirog M, Poliwczak AR, Duchnowicz P, Koter-Michalak M, Sikora J, Broncel M. Melatonin treatment improves blood pressure, lipid profile, and parameters of oxidative stress in patients with metabolic syndrome. J Pineal Res. 2011;50(3):261-6.