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The Impact of Shift Work-Related Circadian Rhythm Disruption on Inflammatory Biomarkers

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ABSTRACT

OBJECTIVE: This study aimed to examine the effect of circadian rhythm disruption in night-shift workers on systemic biomarkers of inflammation. METHODS Demographic data, clinical parameters and data on working patterns of 126 adult employees were documented. Serum levels of biomarkers were measured by enzymatic assay procedures.

RESULTS: Night-shift workers had markedly lower anti-inflammatory IL-10 and cardioprotective adiponectin and MCP-1 compared to daytime workers. Night-shift workers' MIF, LAR, TNF-α and TNF-α/IL-10 ratio were significantly higher than those in day shift workers. Spearman's correlation showed that MIF, TNF-α, LAR and TNF-α/IL-10 ratios were positively and significantly correlated with both the duration of the night shift and total number of shifts ($p < 0.05$). Meanwhile, IL-10, adiponectin and MCP-1 were negatively and significantly correlated with both variables ($p < 0.05$).

CONCLUSION: Night shift work may be closely associated with a higher propensity of cardiometabolic risk factors clustering. Therefore, close monitoring of shift workers' clinical status and lifestyle is warranted.

Keywords: Night shift work, MIF, TNF-α/IL-10 ratio, IL-6, MCP-1, Leptin/Adiponectin ratio.

1. INTRODUCTION

In industrialized countries worldwide, shift workers represent nearly 20% of working adults.[2] Circadian rhythm disruption, such as that caused by chronic shift work, is an established risk factor for several diseases.[1] It has been linked to fatigue, sleep disruption, depressive symptoms, cardiovascular disease, cancer and autoimmune diseases, among other health conditions.[1] Altered clock gene expression and shift work are considered novel risk factors for cancers of the colon, endometrium, prostate, breast, and lymphatic system.[3] The prevalence of cardiovascular risk factors such as obesity, hypertension, hypertriglyceridemia, metabolic syndrome. Consequently, increased risk of cardiovascular disease are reported to be greater in shift workers than in daytime workers.[4] Recently, inflammation has been described as a major player in the pathogenesis of these diseases [5-7].

Sleep disorders such as sleep loss and sleep apnea have been associated with inflammatory responses such as increased leukocyte counts and levels of tumor necrosis factor-alpha (TNF-α), C-reactive protein (CRP) and interleukin-6 (IL-6).[8] Shift work-related circadian disruption has been reported to be strongly associated with increased systemic inflammation.[9,10] While TNF-α has deteriorative effects during the systemic inflammatory

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response, IL-10 has been reported to provide a protective effect.[11] Some studies suggest that a larger TNF-α/IL-10 ratio might act as a predictor of increased risk of complications in patients with inflammatory diseases.[12] To our knowledge, the effect of shift work-related circadian disruption on TNF-α/IL-10 ratio has not been investigated.

The levels of leptin and adiponectin also exhibit diurnal rhythm.[13] They are considered to be two of the best studied adipokines that have been linked to insulin resistance and inflammation. Increased levels of leptin have been shown to be associated with higher levels of CRP, and are predictive of future cardiovascular events.[14,15] Alterations in the sleep-wake schedule have been reported to be associated with an increased daily range of circulating leptin, with the lowest amount of leptin upon awakening. This has been linked to the increased prevalence of obesity in the shift work population.[18] Lower plasma adiponectin levels, on the other hand, are associated with higher levels of CRP, and have been linked with coronary artery disease.[16] Rising evidence suggests that the leptin-to-adiponectin ratio (LAR) correlates with insulin resistance better than either leptin or adiponectin levels alone.[17]

The main aim of this cross-sectional study was to investigate any association between shift work and serum levels of a wide range of biomarkers of inflammation: adiponectin, leptin, LAR, macrophage migration inhibitory factor (MIF), IL-10, IL-6, monocyte chemoattractant protein-1 (MCP-1), TNF-α and TNF-α/IL-10 ratio.

PATIENTS, MATERIALS & METHODS

Study Design and Participants

The study was a part of a larger study designed to investigate the effect of shift work on cardiovascular risk among employees at the University of Jordan Hospital. The study was conducted from June to December 2014. Subjects were selected using a convenience sampling technique. The inclusion criteria were the following: apparently healthy adults ≥ 18 years of age, permanently employed at the same organization for ≥ 3 years, and able to fast for 9 hours prior to obtaining blood samples. Subjects were excluded if pregnant or working only part-time. Overall, 160 subjects were recruited, of which two did not meet the inclusion criteria and 18 refused to participate in the study, resulting in 140 participants. However, 14 subjects were later excluded due to a lack of a sufficient number of samples to perform the required measurements, resulting in a total of 126 subjects actually included in the study.

Participants were classified according to their working conditions into shift workers (shift B (4:00 pm- midnight) and shift C (midnight-7:00 am)) and daytime workers. Shift workers were defined as those engaged in shift work from 4:00 pm until 7:00 am at least four times per month. Daytime workers were defined as those working from 7:00 am until 4:00 pm for at least five days per week for a minimum of three consecutive years. Daytime workers should not have had any previous shift work during their previous working schedule.

Data Collection

Pharmacists were trained to conduct data collection in a consistent manner to decrease the risk of assessment bias. Sociodemographic data and information about working conditions were assessed for all enrolled subjects. A physical examination was performed for all participants to measure height, weight, blood pressure and waist circumference. The waist circumference was measured using a flexible measuring tape that was placed at the midpoint between the upper part of the iliac crest and lower ribs, and the measurement was taken at the end of a normal expiration while the subject stood upright with feet together and arms placed freely at the sides of the body. Blood pressure (BP) was measured using a mercury sphygmomanometer from the participant's right arm in sitting position after 5 minutes of rest. A second blood pressure measurement was obtained after 24 hours, and an average of both readings was used in the analysis.

Measurement of Inflammatory Markers

Commercially available human ELISA assays of serum leptin, MCP-1 (Abcam®, Cambridge, UK), adiponectin, IL-6, IL-10, TNF-α, (eBioscience®, San Diego, USA) and MIF (AssayBiotech®, San Diego, USA) were performed according to manufacturers' instructions. The LAR was calculated by dividing leptin by adiponectin levels, and the TNF-α/IL-10 ratio was calculated by dividing TNF-α by IL-10 levels.

Ethical Considerations

This study was conducted according to the ethical standards outlined in the Declaration of Helsinki.[19] The study protocol was approved by the Institutional Review Board Committee at the Jordan University Hospital on 27 May 2014 (Reference number: 107/2014). All participants provided verbal informed consent prior to enrollment. Participant confidentiality was preserved throughout the study.

Statistical Analysis

All data were entered and analyzed using SPSS© 20 (SPSS, Inc., USA). Categorical variables were expressed as frequencies and percentages, and continuous variables were presented as medians and interquartile ranges (IQR). To evaluate the differences between groups for the clinical parameters of systolic blood pressure (SBP), diastolic blood pressure (DBP), body mass index (BMI) and waist circumference (WC), the Mann-Whitney U test was used for continuous variables, and the chi-square (χ^2) test for categorical variables. When not normally distributed, the levels of inflammatory markers were log transformed. For the comparison of biomarkers between the study groups, a multivariate one-way analysis of covariance (MANCOVA) was conducted, adjusting for the differences in sociodemographic characteristics between the two study arms. Checking for multicollinearity, outliers, normality and linearity were carried out using the methods described by Tabachnick and Fidell.[20] For all statistical analyses, a *p*-value of less than 0.05 was considered statistically significant. All tests were two-tailed.

RESULTS

Daytime and night-shift workers were compared in terms of their demographic and clinical characteristics (Tables 1 and 2). We included 126 subjects in our analysis, of which 80 (63.5%) were females. Females comprised 77.2% of daytime workers, which was significantly higher (p <0.050) than their percentage in shift workers (52.2%). The median age for the entire sample was 30 years (IQR: 27-35.2); however, the median age of daytime workers was significantly higher ($p < 0.001$) than that of night-shift workers. In addition, there was a statistically significant difference in education level between the two study arms. SPB, DBP, BMI and waist circumference were not significantly different between the two groups.

Table 3 shows the median levels and IQR of inflammatory markers in daytime and night-shift workers. MIF, LAR, TNF-α and the TNF-α/IL-10 ratio were significantly higher in night-shift workers than in daytime workers. On the other hand, IL-10 and adiponectin (anti-inflammatory cytokines), as well as MCP-1 were significantly lower in night-shift workers. There were no significant differences in the levels of leptin and IL-6 between the two groups.

As shown in Table 4, Spearman's correlation revealed that MIF, LAR, TNF-α and the TNF-α/IL-10 ratio correlated positively and significantly with both the duration of night shifts and the total number of shifts ($p <$ 0.05). Meanwhile, IL-10, adiponectin and MCP-1 correlated negatively and significantly with both variables ($p < 0.05$). On the other hand, neither IL-6 nor leptin showed any significant relationship with these two variables.

Table 1. Baseline demographics of daytime *vs.* night-shift workers

	All (n=126) N(%)	Daytime (n=57) N (%)	Night-shift (n=69) N(%)	*p*-value[a]
Age[b] (years)	32.15 (27.5-35.5)	34 (29.5-38.0)	29 (27.0-37.0)	0.000*
Gender				
Male	46 (36.5)	13 (22.8)	33 (49.3)	0.002*
Female	80 (63.5)	44 (77.2)	36 (50.7)	
Occupation				
Medical Field	97 (77)	40 (70.2)	57 (82.6)	0.136
Other	29 (23)	17 (29.8)	12 (17.4)	
Income				
High	4 (2.4)	0 (0)	4 (4.3)	0.19
Medium	110 (88)	49 (87.5)	69 (88.4)	
Low	12 (9.6)	7 (12.5)	5 (7.2)	
Marital status				
Single	32 (26)	10 (17.9)	22 (32.8)	0.10
Married	90 (73.2)	46 (82.1)	44 (56.7)	
Divorced	3 (0.8)	0 (0)	3 (1.5)	
Education				
High school	49 (38.9)	34 (59.6)	15 (21.7)	0.000*
BSc or more	77 (61.1)	23 (40.4)	54 (78.3)	
Active smoking				
Yes	28 (22.2)	9 (15.8)	19 (27.5)	0.114
No	98 (77.8)	48 (84.2)	50 (72.5)	
Performing exercise[c]				
Yes	42 (33.3)	14 (24.6)	28 (40.6)	0.06
No	84 (66.7)	43 (75.4)	41 (59.4)	

[a] Calculated by the chi-square test. *Significant at $p < 0.05$,
[b] Age displayed as median (IQR)
[c] Exercise status is only considered moderate in subjects doing physical activity of any kind for at least 30 minutes per day, three times weekly

Table 2. Clinical characteristics of daytime *vs.* night-shift workers as medians (IQR)[a]

Variable	Daytime (n=57)	Night-shift (n=69)	*p*-value[a]
SBP (mmHg)	117 (109.3-122)	116 (108.5-126.0)	0.548
DBP (mmHg)	76 (70.3-80.3)	75 (68.5-83.5)	0.179
BMI (kg/m^2)	24.9 (22.3-28.7)	24.7 (22.5-29.0)	0.986
WC (cm)	90 (80.5-98.0)	87.5 (78.0-98.0)	0.450

[a] IQR: interquartile range; SBP: systolic blood pressure; DBP: diastolic blood pressure; BMI: body mass index; WC: waist circumference. [b]Calculated by the Mann-Whitney U test. *Significant at $p < 0.05$.

Table 3. Levels of inflammatory biomarkers in daytime and night-shift workers as median (IQR)[a]

Biomarker	Daytime (n=57)	Night-shift (n=69)	*p*-value[b]
Adiponectin (ng/mL)	74.9 (58.4-91.4)	36.9 (28.9-51.1)	0.000*
IL-6 (pg/mL)	5.5 (4.8-7.4)	5.0 (3.5-7.4)	0.456
IL-10 (pg/mL)	5.4 (5.1-6.4)	2.6 (1.4-4.0)	0.000*
LAR	0.37 (0.26-0.76)	0.80 (0.50-1.60)	0.002*
Leptin (ng/mL)	27.3 (17.0-52.8)	30.8 (18.6-58.7)	0.570
MCP-1 (pg/mL)	110 (87.1-186)	86.0 (61.0-132)	0.002*
MIF (ng/mL)	2.2 (1.0-5.0)	5.3 (3.9-6.7)	0.003*
TNF-α (pg/mL)	9.6 (6.2-13.6)	16.6 (14.2-19.6)	0.000*
TNF-α/IL-10 ratio	1.6 (1.1-2.4)	6.9 (4.2-12.7)	0.000*

[a] IQR: interquartile range; MIF: macrophage migration inhibitory factor; IL-10: interleukin-10; LAR: leptin-to-adiponectin ratio; IL-6: interleukin-6; MCP-1: monocyte chemoattractant protein-1; TNF-α: tumor necrosis factor-alpha.
[b] Calculated by MANCOVA. *Significant at $p < 0.05$.

Table 4. The correlation between the duration of night shift work and the total number of shifts with inflammatory markers[a]

Biomarker	Correlation[b] with duration of night shift (ρ)	Correlation[b] with total number of night shifts (ρ)
Adiponectin (ng/mL)	-0.539*	-0.493*
IL-6 (pg/mL)	-0.179	-0.103
IL-10 (pg/mL)	-0.483*	-0.471*
LAR	0.327*	0.338*
Leptin (ng/mL)	0.006	0.076
MCP-1 (pg/mL)	-0.209*	-0.190*
MIF (ng/mL)	0.442*	0.434*
TNF-α (pg/mL)	0.541*	0.594*
TNF-α/IL-10 ratio	0.659*	0.659*

[a] MIF: macrophage migration inhibitory factor; IL-10: interleukin-10; LAR: leptin-to-adiponectin ratio; IL-6: interleukin-6; MCP-1: monocyte chemotaattractant protein-1; TNF-α: tumor necrosis factor-alpha; [b]Spearman's correlation coefficient (ρ) *Significant at $p < 0.05$.

DISCUSSION

The purpose of this study was to examine the effect of circadian rhythm disruption in night-shift workers on systemic biomarkers of inflammation, namely, adiponectin, leptin, LAR, MIF, IL-10, IL-6, MCP-1, TNF-α, and TNF-α/IL-10 ratio. In general, night-shift workers showed higher levels of most of the studied inflammatory markers.

Recent studies have evaluated the association between different types of bioactive markers with inflammation. Adipokines are peptides which are released from the adipose tissue and include TNF-α, IL-6, MCP-1, leptin and adiponectin. Increased levels of leptin have been shown to be associated with higher levels of CRP, and are predictive of future cardiovascular events.[14-15] Liang et al.,[21] found that 59 subjects with combined metabolic syndrome (MetS) and cardiac syndrome had a higher circulating leptin level, but a lower circulating adiponectin level than those without such syndromes.

Inflammation is believed to play a major role in the pathogenesis of cardiovascular diseases,[22] Recently, inflammation has been considered one of the hallmarks of cancer, and different types of inflammation have been

shown to contribute to tumorigenesis.[23] Leptin and adiponectin have been suggested to play a role in several types of cancer, such as pancreatic ductal adenocarcinoma.[24-25] Studies have shown a role of leptin in increasing cell proliferation and survival via its receptor (OB-Rb) in colon, ovarian, breast, endometrial and androgen-insensitive prostate cancer cells.[26-27] On the other hand, adiponectin has been reported to inhibit the proliferation of several types of cancer cells.[28-29] The LAR was found to be higher in cancer patients compared to healthy and diabetic patients.[30] Importantly, increased LAR is not only correlated with obesity, but also reported to be involved in neoplastic transformation and tumor progression.[31] In this present study, we found that LAR was significantly higher in night-shift workers compared to daytime workers.

In our study, we compare the level of leptin, adiponectin, LAR in addition to a wide range of inflammatory markers (MIF, IL-10, IL-6, MCP-1, TNF-α and TNF-α/IL-10 ratio) in night-shift versus day-shift workers. The levels of leptin were not significantly different between the two groups; nevertheless, its levels tended to be higher in night-shift workers as well. On the other hand, adiponectin was significantly lower in night-shift workers compared to daytime workers; accordingly, LAR was significantly higher in night-shift workers. Although the levels of leptin tended to be higher in shift workers, this difference was not statistically significant. To our knowledge, only few inconclusive studies have investigated the effect of shift work on these adipokines. It has been previously reported that weeks of circadian misalignment resulted in lower leptin levels.[32] However, in another study, the levels of leptin and adiponectin were shown to not be significantly different in shift workers compared to daytime workers.[33] Gasier et al.,[34] studied the effect of limited exercise equipment, confined space, rotating shift work and reduced sleep on cardiometabolic health in submariners. TNF-α, MCP-1, MIF and TNF-α/IL-10 ratio were all significantly higher in night shift workers compared to daytime workers. However, the LAR for those submariners was similar to that before the 3 months submergence.[34]Higher levels of these inflammatory cytokines have been reported to increase the risk of type 2 diabetes, cancer, asthma, cardiovascular disease, Parkinson's disease and cognitive impairment.[5] Studies have shown that higher TNF-a/IL-10 ratios may act as a predictor of increased risk of complications in patients with inflammatory diseases.[12] Moreover, high TNF-α/IL-10 ratio has been associated with several health issues such as cancer and coronary artery diseases.[35-36]

Although shift work has been reported to be strongly associated with increased systemic inflammation,[9-10] field studies cannot definitively confirm a causal role of circadian misalignment related to shift work to poor health consequences. The cause of these consequences may be multifactorial, due to factors such as genetics, overall health, work environment, physical activity, eating habits and social factors. Three laboratory studies, however, have investigated the impact of circadian misalignment on inflammatory markers in humans.[37-39] One of these studies concluded that the effect of shift work on inflammatory response was independent of sleep loss.[37] Wright et al.,[39] on the other hand, reported increased levels of CRP, TNF-α and IL-10 in circadian misalignment. In a highly controlled experimental protocol, Morris et al.,[38] showed the influence of circadian misalignment on cardiovascular and inflammatory risk factors by controlling for other potential factors that might interfere with such conditions. The authors found that circadian misalignment increased the inflammatory markers CRP, TNF-α, resistin, and IL-6, suggesting that it serves as an underlying mechanism to explain the association between shift work and both hypertension and cardiovascular disease.[38] In our study, the results were consistent with these findings and confirm the relationship between shift work and a wider set of inflammatory markers.

It is important to mention that there were several limitations to our study, including the relatively small sample size and the strict inclusion criteria of night shift workers. Night-shift workers had to be working from 4:00 pm until 7:00 am at least four times per month for at least three years. This resulted in a limited number of

individuals meeting these criteria. The fasting requirements sometimes required that shift workers fast during their shift work which proved to be challenging. In addition, we did not collect data about the dietary habits of the participants, a factor that may have affected the biomarkers studied. We also did not collect data on shift sequence, rotations or number of days off, which also may have confounded the results for the markers of interest. However, to account for this, we correlated levels of inflammatory biomarkers with the duration and total number of night shifts (Table 4). Finally, since this study was cross-sectional in design with nonrandom sampling, we could not infer a causal relationship between shift work and increased circulating inflammatory biomarker levels. However, our results were consistent with other study results that did account for such potentially confounding variables and studies that confirmed a causal association.[37-39]

CONCLUSION

Our findings demonstrate differences in the levels of inflammatory markers shift workers and daytime workers, which are a cause for alarm given that these differences are associated with poor health consequences. The results support the need to modulate such risk in shift workers, especially since ***shift work*** is steadily increasing in modern society. Targeting the LAR through weight loss, dietary changes and pharmacological interventions for prevention of many health problems such as cancer has been suggested.[40] Although many epidemiological studies have demonstrated that lack of sleep may be closely related to the incidence of obesity, our study the alarming clustering of cardiometabolic anomalies in lean night shift workers. Our results suggest that night shift work may cause negative changes in inflammatory biomarkers, possibly through misalignment of the circadian rhythm. Future investigations on the effect of night shift work on the molecular cross talk among metabolic, neuroendocrine and antioxidant biomarkers are suggested for the same pool of lean participants.

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اضطراب النظم اليومي في العاملين في المناوبات الليلية على العوامل الحيوية الالتهابية

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ملخص

الهدف: تهدف هذه الدراسة إلى دراسة تأثير اضطراب النظم اليومي في العاملين في المناوبات الليلية على القياسات البشرية (الأنثروبومترية) والعوامل الحيوية الالتهابية.

التصميم: تم توثيق البيانات الديموغرافية، والمعايير السريرية، وأنماط العمل لمئة وستة وعشرين من الموظفين البالغين وتم قياس مستويات المؤشرات الحيوية من خلال إجراءات الفحص الأنزيمي.

النتائج: يرتبط العمل بالمناوبة الليلية بشكل وثيق مع الميل العالي لمجموعة عوامل خطر الأيض القلبي. كان مستوى المضادة للالتهابات IL-10 وأديبونيكتين و MCP-1 أقل لدى العاملين بمناوبات ليلية. كانت مستويات MIF و TNF-α, LAR, ونسبة TNF-α/IL-10 أعلى بكثير مما كانت عليه في العاملين خلال النهار. كما أظهرت علاقة سبيرمان أن مستويات MIF و TNF-α و LAR ونسبة TNF-α/IL-10 ترتبط ارتباطا إيجابيا وكبيراً مع كل من مدة العمل بالمناوبة الليلية وعدد المناوبات الاجمالي ($p < 0.05$). وفي ذات الوقت يرتبط IL-10، أديبونيكتين، IL-6 و MCP-1 سلبا وبشكل ملحوظ مع كل من المتغيرين ($p <0.05$).

الاستنتاجات: يمكن أن يرتبط العمال بالمناوبات الليلية بشكل وثيق مع الميل العالي لمجموعة عوامل خطر الأيض القلبي مما يبرر ضرورة الرصد الدقيق لحالتهم السريرية وأسلوب حياتهم.

الكلمات الدالة: المناوبات الليلية، العوامل الحيوية الالتهابية.

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