Serum Level of Cortisol, hsCRP and IL-6 in Depressed Rotational Shift Workers

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ABSTRACT

Background: Depression and sleep disorders are more prevalent among rotational shift workers than regular day workers. People with sleep disorders have higher inflammatory and pre-inflammatory cytokines than those in the control group.

Objectives: The present study was conducted to investigate serum level of high sensitivity C-reactive protein (hsCRP), Interleukin-6 (IL-6) and cortisol among depressed rotational shift workers at Iran petroleum industry.

Materials and Methods: In this cross sectional study, 136 shift workers were studied based on the inclusion and exclusion criteria. Demographic information was collected using a self-administered general questionnaire and depression score was gathered according to 21-question Beck depression inventory. Also, weight and height were measured to calculate body mass index and history of disease was collected based on their occupation profile at health center of Tehran Shahid Tondgoyan oil refinery.

Results: Mean and standard deviation of serum concentration of hsCRP, IL-6 and cortisol were 1.03 ± 1.56, 1.24 ± 1.24 and 13.12 ± 3.93 respectively; while mean and standard deviation of depression score and BMI were 14.07 ± 3.84 and 24.92 ± 3.65, respectively. Depression score had a positive correlation with rotational shift work experience and work experience ($r = 0.218$ and $r = 0.212$, respectively, $P < 0.05$). An inverse relation was found between serum concentrations of cortisol and age, work experience and BMI ($r = -0.236$ and $P < 0.05$, $r = -0.174$ and $P < 0.05$, $r = -0.288$ and $P < 0.05$, respectively). IL-6 and hsCRP had a positive relation with each other ($r = 0.616$, $P < 0.001$). Serum concentration of hsCRP had a positive correlation with BMI ($r = 0.241$, $P < 0.01$).

Conclusions: There was no significant correlation between depression score and inflammatory markers among depressed shift workers. However, depression score had a significant correlation with shift work experience.

Keywords: Depression; Hydrocortisone; Cytokines

1. Background

Shift work is the work done in periods other than conventional working hours (7 am to 6 pm) (1). In order to make better use of economic resources and compete with other industries and meet the need for more production, it is essential for many industries such as refineries to have 24-hours work pattern. More than twenty to thirty percent of workers are shift workers (2). In shift workers, deviation from the daily work pattern -activity/sleep- leads to the disturbance of their bodily rhythmic and physiological activities which is known as circadian rhythm (3).

Circadian system is completely influenced by ambient light in human being (4, 5) and the restriction of light during the day is the main reason that shift workers, even night shift workers, may never adapt with their sleep/activity cycle, which is necessary for their work shift (6-8). Shift work negatively impacts workers' health condition (9, 10) and causes disorders that force workers to leave their jobs more often in rotational shift workers in comparison with night or day workers. Among the health problems caused by shift work are depression and sleep disorder. The prevalence of difficulty initiating sleep is higher in rotational shift workers compared to regular day workers (9, 11).

Shift workers have more excessive sleepiness and disturbed sleep compared with regular day workers and these disorders are more common among them (12). Ten to ninety percent of shift workers complain about sleep disorder and insufficient sleep (13), which depends on factors including speed and direction of shift rotation (14, 15). Furthermore, sleep deprivation and occupational stress lead to immune inflammatory responses, determined by increased pre-inflammatory cytokines (16).

In other words, during the day, pathophysiological complications of sleep deprivation such as increased level of pre-inflammatory cytokines in blood causes more sleepiness and reduces neurobehavioral function consequently, depression increases (17) and changes hormonal level (18). CRP and IL-6 are among inflammatory and pre-inflammatory markers which increase in sleep deprivation and are also considered as the risk factors of most diseases such as depression (19). Cortisol is not only a very powerful marker in circadian cycle, but also is used as a criterion for determining stress (20, 21). Under normal conditions, cortisol level is high during the day and decreases at night.

Lack of balance in cortisol level causes exhaustion, depression and malfunction of immune system . Cortisol secretion is less in the morning and higher at night among night shift workers when compared with those who are permanent day workers (22).

There is overwhelming evidence to indicate that major depression is associated with inflammatory response indexed by elevation of CRP and other cytokines such as IL-6 and TNF alpha (23). Adoption to chronic stress involves both responses from neuro-endocrine and immune system that result in alteration of cortisol release. On the other hand, systemic inflammation characterized by high concentrations of inflammatory cytokines, may play a role in pathophysiology of depressive disorders (24).

2. Objectives

This study was conducted to investigate concentrations of cortisol, IL-6 and hsCRP among depressed rotational shift workers who work at Oil Refinery industry.

3. Materials and Methods

3.1. Participants

In this cross-sectional study, 456 potentially eligible candidates were screened and a total of 397 workers returned the questionnaires. One hundred and one subjects did not meet the inclusion criteria. One hundred and sixty one subjects were excluded from the study due to smoking or having other chronic diseases. Finally, 136 shift workers aged 21-51 years, who met the inclusion criteria were enrolled in the study.

The inclusion criteria included depression score ≥ 10 in Persian version of the Beck depression rating scale-21 items and their consent to participate in the study as well as the wash-out periods of two months for antidepressants and two weeks for supplements prior to entry. The exclusion criteria also included any positive history of thyroid, liver or renal disorders, diabetes, cardiovascular diseases, cancer and hypertension. Occupational profiles, performing professional sports, smoking, consuming alcohol and substance abuse were collected using a self-administered general questionnaire.

Noteworthy, all shift workers at Tehran Shahid Tondgoyan oil refinery were men and their program was 8-hours backward shifts (from night to morning) indicated as four nights, three off, four afternoon, one off, four morning (NNNNOOOAAAAOMMMM). This study was confirmed by committee of medical ethics, faculty of medicine of Tarbiat Modares university, Tehran, Iran. Prior to entering the study, all participants provided informed written consent.

3.2. Procedure

Data collection was performed using self-administered general questionnaire and the persian version of 21-question Beck depression inventory (25). This edition of translated questionnaire has a high internal consistency (Cronbach's α = 0.87) and accepted test-retest reliability (r = 0.74) (26). The general questionnaire included questions on age, marital status, work experience, shift work experience, education, sports, smoking, alcoholic drinks,

narcotics, drugs and complementary drugs. Depression score of the participants was measured using 21-items Beck depression inventory at the beginning of the study. After obtaining a detailed medical history, physical examination was performed by the interviewing physician. Height was measured with subjects standing in front of a standard SECA height gauge (Germany) and the nearest 0.1 centimeter was recorded. Weight was measured with subjects having only light clothing on and was recorded with 0.1 kilogram precision (SECA, Germany). BMI was then calculated as follows: Weight in kilograms divided by height in square meters. After sitting for at least 10 minutes, two readings of systolic and diastolic blood pressures were obtained from each participant with five minutes interval, employing a standard sphygmomanometer (Riester, Big Ben adults, Germany).

3.3. Laboratory Evaluations

To measure concentrations of hsCRP and IL-6, from 7.30 am to 8.30 am, 8 ml blood sample was obtained from the anterior cubital vein at sitting position and after fasting for 10-12 h. Needle holder 21 in a gel-containing tube without anti-coagulant (Behdarou Company) was used. Then, serum was separated using centrifugation for about 10 min at 1500 rpm. The extracted serum was transferred to microtubes labeled for the participants and was kept at -70 °C until the analysis time. Cortisol, IL-6 and hsCRP were measured using

RIA kit in radioimmunoassay method (R and D Germany and Pars Azmoon company, respectively). Inter- and intra-assay coefficient of variation of employed kits for measurement of cortisol concentrations were < 9.2% and < 5.8 respectively. Intra- and inter-assay precisions were < 5% and < 10% respectively, for remaining parameters (IL-6 and hsCRP).

3.4. Statistical Analysis

All statistical analyses were performed using SPSS version 19.0 (IBM Corporation, New York, United States). Continuous variables are expressed as mean ± standard deviation. The relation between quantitative variables was tested by Pearson correlation coefficient. In all tests, P value < 0.05 was considered statistically significant.

4. Results

All of shift workers were men and participants' age ranged from 21 to 51 years old. *Table 1* presents baseline characteristics of the participants. Among the subjects, majority of them (90.4%) had mild depression (depression score of 10-18 according to Beck depression inventory) and 9.6% had average depression (depression score of 19-29 according to Beck depression inventory). Socio-demographic information regarding educational level and marital status are also demonstrated in *Table 1*.

Table 1. Baseline Characteristics of the Study Participants

Variables	
Age, y	30.75 ± 7.19
Depression score	14.07 ± 3.84
Marital status (married)	64%
Educational level	
Middle school	2.3%
High school	58.8
Higher than diploma	38.9%
Section working	
Operation section	80.9%
Firefighting section	19.1%
Work experience, y	6.91 ± 6.76
Shift work experience, y	6.14 ± 6.24
BMI, kg/m²	24.92 ± 3.65
Systolic Blood Pressure, mmHg	110 ± 12.1
Diastolic Blood Pressure, mmHg	88.84 ± 10.81
Serum cortisol, microg/L	13.12 ± 3.93
Serum hsCRP, mg/L	1.02 ± 1.52
Serum IL-6, pg/mL	1.24 ± 1.24

Abbreviation: HsCRP, highly sensitive C-reactive protein

Among subjects, 80.9% of the participants were working in operation section, meanwhile 19.1% were fire fighters.

Two point three percent of subjects had educational level of guidance school, 58.8% had high school diploma, and the re-

maining (38.9%) had higher educational level. Mean of work experience was 6.91 ± 6.76 years, while mean of shift work experience was 6.14 ± 6.24 years. Mean and standard deviation of serum inflammatory markers are illustrated in *Table 1*. In included subjects, average of serum cortisol concentrations was 13.12 ± 3.93. These figures were 1.02 ± 1.52 and 1.24 ± 1.24 for serum hsCRP and IL-6, respectively. In this survey there was a significant association between depression score and both duration of work experience and shift work experience (r = 0.212 and r = 2.18, respectively, P < 0.05). An inverse relation was found between serum level of cortisol and age, work experience and BMI (r = -0.236 and P < 0.05, r = -0.174 and P < 0.05, r = -0.288 and P < 0.05, respectively,). IL-6 and hsCRP had a positive relation with each other (r = 0.616, P < 0.001).

Depression score was not correlated with any of serum inflammatory markers (P value 0.95, 0.24, and 0.57 for IL-6, cortisol ,and hsCRP ,respectively). Therefore, our results did not demonstrate any significant association regarding inflammatory state and depression score.

5. Discussion

Some studies have shown that depression and sleep disorders are more prevalent among rotational shift workers than regular day workers (11, 27, 28). Other studies have also demonstrated that people with sleep disorders have higher inflammatory and pre-inflammatory cytokines than those in the control group (16, 19).

A study in patients with major depressive disorder (MDD) proved that its frequency was higher in married people compared to the single. Furthermore, most of them had high school diploma or higher education (29). The results are in agreement with the results of the present study. In the present study, 64% of the depressed participants were married and 58.8% had high school diploma. Also, depression score had a positive relation with shift work experience. Thereby, such results are consistent with the results of previous studies (30).

In a study which was performed among 45 shift workers in a factory on the second shift of the day, showed that the mean value of cortisol was 12.5 nmol/L 30 minutes after their wake-up time. Also, there was a significant difference between serum level of cortisol in day worker (17.5 nmol/L) and shift workers (31). Axelsson et al. (31) demonstrated that in rapid rotational shift working, cortisol level decreased in the morning which could be attributed to the down regulated hypothalamus-pituitary-adrenal (HPA) axis in accordance with the long-term stress.

As mentioned before, previous studies have shown that the majority of shift workers have sleep disorders. In another study, 14 patients with sleep disorders with mean age and standard deviation of 46.8 ± 7.3 years and BMI of 22.9 ± 3 had a cortisol level of 12.2 ± 5.5 nmol/L 15 minutes after wake-up, which was less than that of the control group (15.3 ± 3.4 nm/L) (31). Furthermore, some epidemiologic studies have reported that the risk of depression is high among patients with insomnia (32) and cortisol increment in the morning is common among depressed patients (33). Therefore, shift working leads to cortisol reduction in the mornings due to sleep disorders and on the other hand, depression increases cortisol level which is approximately in line with the results of the current study. In this study, cortisol concentration was less than that of permanent day workers and was a little more than that of shift workers compared to previous studies.

A study on 22 healthy men showed that waist to hip ratio had an inverse correlation with cortisol level (34). In another study, 129 women from 11 rural industrial sites in North Carolina were investigated and an inverse relation was found between cortisol and BMI (35). Such inverse relation between serum cortisol level and BMI are in line with our results. In the present study, cortisol had an inverse relation with age and shift work experience. In a study, this relation was positive among obese people (35) and in another study, no relation was found between cortisol and age among 25 patients with major depression after recovery. Taking into account the findings of the previous studies, the results are inconsistent for different populations and conditions. In the present study, this relation was inverse which could be attributed to the different sampling method.

Table 2. Univariate Correlations Between Variables

	IL-6		Cortisol		hsCRP	
	r[a]	P Value	r	P Value	r	P Value
Age, y	0.035	0.687	- 0.236	0.006	0.105	0.226
Work experience, y	0.046	0.599	-.0174	0.042	0.050	0.563
Shift work experience, y	0.053	0.543	-0.136	0.115	0.067	0.438
Depression score	-0.004	0.959	-.0101	0.243	0.048	0.577
BMI	0.152	0.07	-0.28	0.001	0.241	0.005

Abbreviations: BMI, body mass index
[a] r; Pearson correlation

A study on hospital residents with the mean age of 29 years old and long-term working hours (30 h) from 7 am to 1 pm showed that mean IL-6 level was 1.09 pg/mL with the range of 3.15-0.59, and mean hsCRP level was 1.5 mg/L with the range of 0.1-0.3 mg/L, which had a significant difference with that of ordinary workers (7am-1pm) (17). In the aforementioned study, IL-6 and hsCRP had a positive relation with each other. The results are in line with the results of the present study in which hsCRP had a positive relation with IL-6 ($r = 0.616$, $P < 0.001$) (*Table 2*). In conclusion, this study showed that the cortisol concentration in depressive shift workers is lower than that of the general population. Also, cortisol level was inversely correlated with age, work experience and BMI. Therefore, the managers of oil refinery plants should pay more attention to the overweight or fat shift workers and shift workers with long shift work duration in terms of depressive symptoms and inflammatory state. In this regard, physical activity schedules and nutritional interventions may be beneficial.

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Authors' Contributions

SBM conceived the study, participated in its design, coordination and acquisition of data. FKH was involved in recruiting patients and collection of data. FKH and SAKH performed statistical analyses. All authors contributed to patient recruitment and also prepared early draft of the manuscript. FKH revised the early draft. All authors participated in interpretation of the results and editing the manuscript. All authors contributed significantly, read and approved the final manuscript.

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