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Original Article

Study of correlation between chronic stressor, biochemical markers and hematologic indices in Shahrekord Cohort Study: A population-based cross-sectional study

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ABSTRACT

Aim: Stress is one of the most common and controllable risk factors for non-communicable diseases. The purpose of this study was to determine the relationship between stress and biochemical factors and hematologic indices.
Methods: The data to conduct this cross-sectional study were obtained from Shahrekord Cohort Study (SCS). The sample size included 1000 people who were randomly selected from 7000 people enrolled in the SCS conducted in 2017–2018. To measure stress as well as blood biochemical factors and hematologic indices, the Questionnaire of Stressful Life Events and Glucose and Lipid profile were used, respectively.
Results: Among stress dimensions, job security was significantly associated with most biochemical factors and hematologic indices. Linear regression model showed that there was a significant correlation between stress and blood urea, liver enzymes (ALT and AST), education, marital status, and occupation.
Conclusion: This study reported that the level of exposure to stressors was higher than that of other studies, and the results of this study are recommended to be used for screening and early detection of the consequences of exposure to chronic stressors, especially for the prevention of cardiovascular diseases.

1. Introduction

Stress is one of the most common and controllable risk factors for non-communicable diseases that are considered to be the main causes of disease burden in the world, region, and Iran [1]. Depression and anxiety are among the most common psychiatric disorders with a prevalence increase of 20% per year in the general population [2]. The complexity of individual and social life requires individuals to constantly cope with adversities [3]. Stress is the body's response to any demand, change, or perceived threat, and the stressor is the state or event that provokes this response [4,5]. Many studies have shown a relationship between psychological factors and coronary artery disease and metabolic diseases [6].

Factors related to stress and stressors do not cause anxiety or stress, but stress occurs as a result of their interaction effects, individual's perception, and organism response [7]. Pathophysiological events that occur due to dealing with prolonged psychological stress in humans cannot be definitively determined, but cause the involvement of the hypothalamic–pituitary–adrenal (HPA) axis as well as the involvement of endocrine glands and the immune system [8,9].

Continued stress can lead to increased blood pressure, insomnia, tachycardia, immunodeficiency, and even reduction in life expectancy [10]. The results of the research have shown that the psychological states of the individual can affect the blood levels of lipids. It is likely that stress increases the activity of the sympathetic nervous system by increasing the activity of adrenalin in the blood, and also increases the blood levels of lipids by influencing the lipoprotein lipase and hepatic lipase [11]. It is therefore likely that stress will be effective in developing cardiovascular diseases. In

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addition, poor control of diabetes and stressful events of life have a significant positive correlation with each other, and small stresses in everyday life are even more associated with poor metabolic control than important and significant stresses [12]. Cortisol secretion is one of the body responses to stressors [13]. Cortisol, which has an effect on the liver, increases the production of sugar and reduces its use in the tissues of the body [14].

The relationship between stresses and other biochemical and hematologic factors has not yet been adequately explained and few studies have been conducted on this issue.

No population-based study has yet been conducted in Chaharmahal and Bakhtiari province, southwest of Iran, to achieve this purpose. The purpose of this study was to investigate the relationship of stress with biochemical factors and hematologic indices as well as their efficacy for screening and early detection of the consequences of exposure to chronic stressors.

2. Materials and methods

2.1. Participants

The data to conduct this descriptive-analytical, cross-sectional study were obtained from a prospective population-based study, namely Shahrekord Cohort Study (SCS). This study was designed to serve as one of the centers of the Prospective Epidemiological Research Studies in IrAN (PERSIAN) Cohort and is being conducted in Chaharmahal & Bakhtiari province, southwest of Iran. That cohort of people aged 35–70 years started in November 2015 in Iran. The sample size of the original cohort is at least 10000 people. Further information is available at http://cohort.skums.ac.ir and protocol of the study [15].

2.2. Data collection

The sample size included 1000 people who were randomly selected out of 7000 ones enrolled in the SCS conducted in 2017–2018. In this study, dependent variable was stress and independent variables were age, sex, education level, job, marital status, body mass index (BMI), biochemical factors alanine aminotransferase [1,16], aspartate aminotransferase [17], alkaline phosphatase (ALP), fasting blood sugar (FBS), triglyceride (TG), cholesterol (Chol), low-density lipoprotein (LDL), high-density lipoprotein (HDL), creatinine (Cr), and blood urea and hematologic indices [white blood cell (WBC) and red blood cell (RBC) count, hemoglobin (HGB), hematocrit (HCT), mean corpuscular volume (MCV), nean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), platelet, and red cell distribution width (RDW-CV)].

The Questionnaire of Stressful Life Events (SLE) was employed to assess the frequency and the perceived intensity of various life stressors. 46 items of the questionnaire covered 11 stress domains consisting of home life, financial problems, social relations, personal and job conflicts, educational concerns, job security, loss and separation, sexual life, daily life, and health concerns. Each item was scored by using a 6-point Likert scale (Never = 0, Very low = 1, Mild = 2, Moderate = 3, Severe = 4, and Very severe = 5). Total intensity score indicates perceived intensity of stressors. Higher scores represent higher perception of stress intensity. Moreover, the frequency of each stressor and the total stress frequency were determined [18].

The minimum and maximum attainable scores on the questionnaire are zero to 230, respectively. In previous studies, the reliability of this questionnaire has been reported 0.92 by the Cronbach's alpha coefficient [19]. Validity and reliability of the questionnaire were also recalculated in the SCS, and its cronbach's alpha coefficient was obtained 0.85.

To observe ethical considerations, informed consent was obtained from all participants. The data were collected confidentially by a trained questioner in a separate room through interview and questionnaire completion as a quality control officer supervised data collection process.

2.3. Statistical analysis

Data were analyzed by the SPSS version 23. For describing statistics and determining the relationships, mean [± standard deviation [20]] as well as the correlation coefficients, *t*-test, ANOVA, and linear regression model was used. $P < 0.05$ was considered the statistical significance level.

3. Results

Of the 1,000 participants in the study, 430 (43%) were male and 570 (57%) female. The mean (±SD) age of the participants was 50.73 (±9.66) years, most of whom were unemployed (57%), had university education (43.6%), and were married (95.4%). The mean (±SD) BMI was 27.81 (±4.4). The mean (±SD) exposure to chronic stressors in our participants was 34.64 ± 24.48. The mean (±SD) level of stress in men was 34.44 (±24.48), which is higher than that in women (32.5 ± 24), but the difference was not statistically significant ($P = 0.175$). The mean (±SD) level of stress was significantly higher in the single (39.29 ± 38) and divorced (67.83 ± 37) subjects than in the widows/widowers (32.61 ± 25) and the married (33.13 ± 24) ($P = 0.004$).

The mean (±SD) level of stress was higher in the employed people (36.35 ± 25) than in the unemployed (31.2 ± 24), with a significant difference of $P = 0.001$. There was a statistically significant relationship between stress and certain variables such as age, marital status, education level, and occupation ($P < 0.05$). However, there was no significant relationship between sex and BMI ($P > 0.05$). The relationship between the total score of stress and biochemical and hematologic factors was investigated. No significant relationship was found between the overall score of stress and any of the hematologic factors ($P > 0.05$) (Table 1). However, there was a significant relationship between stress and total cholesterol and LDL ($P < 0.05$) (Table 2).

The relationship between the 11 dimensions of stress and biochemical and hematologic factors was investigated. The dimensions of social relations, education concerns, job security, loss and separation, and health problems were significantly associated with FBS ($P < 0.05$). Among dimensions of stress, job security was significantly associated with most biochemical and hematologic factors (Tables 1 and 2). In addition, the dimensions of sexual life and daily life were significantly associated only with RDW-CV and not significantly associated with other biochemical and hematologic factors.

In the linear regression analysis, the relationship between stress and all variables was studied. The results showed that there was a significant correlation between stress and blood urea, liver enzymes (ALT and AST), education, marital status, and occupation. However, stress was not significantly associated with other variables (but also there is a positive correlation between obesity and ALT and LDL. So we need to adjust our finding with BMI, and we excluded patients with high BMI and then analysis the data from stress and ALT, and LDL) (Table 2). The difference between the results of correlation analysis and linear regression analysis between stress and biochemical factors and demographic variables confirms the presence of confounding variables.

Table 1
Correlation between chronic stressors, FBS, and Lipid profile in the survey.

Domain		Stress (Mean ± SD)		p-value
		Male(430N)	Female(570N)	
FBS	70–100	34.3 ± 24	33.5 ± 25	0.22
	101–125	36.9 ± 26	31.5 ± 24	
	≥126	29.9 ± 25	27.1 ± 18	
TCOL	<200	36.1 ± 26	32.9 ± 25	0.16
	200–239	30.9 ± 21	31.9 ± 24	
	≥240	28.1 ± 16	30.6 ± 21	
TG	<150	37.4 ± 25	32.8 ± 25	0.15
	150–199	29.9 ± 18	34.3 ± 24	
	≥200	32.3 ± 26	30.6 ± 23	
HDL	≥40 male,≥50 female	34.36 ± 25	32 ± 25	0.7
	<40 male <50 female	36.9 ± 23	33.3 ± 23	
LDL	<130	35.1 ± 25	32.1 ± 25	0.99
	130–159	29 ± 16	35.7 ± 23	
	≥160	33.8 ± 23	34 ± 26	

Table 2
Analysis of liner regression between chronic stressors and biochemical and hematology markers.

Variable		Mean ± SD/Frequency(%)	Beta	t-value	p-value(2tailed)
Fasting Blood Sugar		99.96 ± 22	-.035	−1.080	.280
Blood Urea		28.66 ± 7	-.110	−3.147	.002
Creatinine		1.12 ± 0.2	.062	1.553	.121
Cholesterol		184.63 ± 32	.763	1.260	.208
Triglycerides		162.98 ± 73	-.426	−1.554	.121
HDL cholestrol		53.43 ± 11	-.234	−1.112	.267
LDL cholestrol		98.81 ± 26	-.649	−1.385	.167
SGOT (AST)		20.45 ± 6	-.090	−1.937	.053
SGPT (ALT)		24.08 ± 13	.106	2.176	.030
Alkaline phosphatase		216.47 ± 57	-.025	-.774	.439
WBC		6.10 ± 1	-.010	-.292	.771
RBC		4.83 ± 0.5	-.138	-.469	.639
HGB		14.71 ± 1	-.173	-.164	.870
HCT		42.71 ± 4	.331	.300	.764
MCV		88.7 ± 6	-.610	-.766	.444
MCH		30.57 ± 3	.555	.647	.517
MCHC		34.43 ± 1	-.030	-.134	.894
PLATELETS		242.34 ± 51	-.032	-.891	.373
RDW-CV		11.29 ± 1	-.021	-.553	.581
AGE		50.73 ± 9	.058	1.613	.107
Last education	illiterate	192(19.2%)	-.081	−2.534	.011
	Diplom	372(37.2%)			
	College education	436(43.6%)			
Marital State	Single	17(1.7%)	.063	1.979	.048
	married	954(95.4%)			
	widow	23(2.3%)			
	divorced	6(0.6%)			
Sex	Male	430(43%)	.029	.786	.432
	Female	570(57%)			
Job Group	Unemployed	570(57%)	.156	3.839	.001
	Employee	430(43%)			
BMI		27.81 ± 4	.049	1.508	.132

4. Discussion

The results of this study showed that, in the linear regression model and after controlling the effect of confounders, there was a significant relationship between stress and blood urea, liver enzymes (ALT and AST), education, marital status, and occupation. The mean (±SD) level of stress in our participants was higher than that in a similar study (28.57 ± 19.86) [13]. The results of the study of Isfahan Healthy Heart Program (IHHP) showed that the relative risk of high levels of stress in the people with high total cholesterol, high LDL, and low HDL levels was 11.1, 1.13, and 1.21, respectively [17].

Our study also showed that high level of stress was significantly associated with cholesterol and LDL. Herd and Dimsdale, in a review article, argued that free fatty acids and total cholesterol increased after acute and chronic stresses [20]. Increased level of triglyceride in the blood of the people with history of stress in the last 12–16 months has also been confirmed in another study [21]. In our study, stress and TG levels were closely associated. In contrast with the results observed in this study, in some studies, individuals with low HDL levels have been reported to experience higher levels of stress than normal people [11,22]. In this study, HDL level was significantly associated with the dimensions of loss and separation and job security. Two meta-analyses in 2013 showed the relationship between job stress and risk factors for cardiovascular diseases. In the first study, eight studies conducted on a total of 47000 subjects were reviewed [23], and in the second study, 13 cohort studies following up a total of 174438 people for 10 years were reviewed [24]. In both meta-analyses, job stress and job insecurity were associated with the onset of type 2 diabetes. Several other studies have also shown that stress and mental stress play an important role in the progression, aggravation, and chronicity of diabetes [25]. The results of the researches have indicated the effect of stress on blood glucose levels. Cortisone released during stressful times accelerates the formation of glucose and glycogenolysis, which results in increased blood glucose [26]. Kuan-Yu Pan et al. investigated the relationship between job stress and type 2 diabetes. The results of the study showed that occupational stress may increase the risk of type 2 diabetes in women in the early 60's [27]. In other studies, blood glucose levels were observed to increase with increasing occupational stress [28,29]. Expecting an increase in blood glucose in people with chronic stress is due to increased energy requirements during chronic stress, but since the range of blood glucose concentrations is always maintained even during fasting days, it is not possible to clearly detect glucose changes [29]. In this study, no relationship between the overall score of stress and FBS was observed, but the dimensions of social relations, education concerns, job security, loss and separation, and health concerns were significantly associated with FBS level. Platelet activity increases in dealing with stress. The results of one study showed that in panic disorder (PD) patients, the MPV and red cell distribution significantly increased. In addition, in this study, WBC level was significantly different between PD patients and controls [16]. However, stress was not significantly associated with platelet and WBC in the present study. There was a statistically significant relationship between the dimensions of job security and job conflict and platelets, and the dimension of loss and separation was only observed to be significantly associated with WBC. The present study reported the level of stress in a population-based cohort study, namely SCS, and showed that exposure to chronic stressors in this population was higher than the results of similar studies. The relationship between different dimensions of chronic stressors and certain biochemical factors was observed in this study. The results of this study are recommended to be used for screening, prognosis, and early detection of the consequences of exposure to chronic stressors, especially for the prevention and control of cardiovascular diseases as the most important causes of mortality in Iran.

Conflicts of interest

There is no conflict of interest regarding this work.

Acknowledgments

The authors would like to gratefully thank participants of this study and authorities of Shahrekord Cohort Study for their sincere cooperation. This study was conducted with observance of the Declaration of Helsinki and the National Ethical Guidelines in Biomedical Research in Iran. Besides, the study protocol was approved by the Ethics Committee of the SKUMS (IR.SKUMS.REC 1396.90) at regional and national scales. All participants provided signed and fingerprinted informed written consents according to the Guidelines enforced by the Ethics Committee of the SKUMS. The participants can withdraw from the study whenever they wish. Data are stored in a codified confidential database. The SCS was funded by Iran's Ministry of Health and Medical Education (number 700/120), to develop cohort studies across Iran, and also was financially and nonfinancially supported by the SKUMS (number 2508).

Abbreviations

SCS	Shahrekord Cohort Study
ALT	Alanine aminotranferease
AST	Aspartate Aminotransferase
HPA	Hypothalamic–Pituitary–Adrenal
BMI	Body Mass Index
ALP	Alkaline Phosphatase
FBS	Fasting Blood Sugar
TG	Triglyceride
Chol	Cholesterol
LDL	Low-Density Lipoprotein
HDL	high-density lipoprotein
Cr	creatinine
WBC	White Blood Cell
RBC	Red Blood Cell
HGB	Hemoglobin
HCT	Hematocrit
MCV	Mean Corpuscular Volume
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
RDW-CV	Red Cell Distribution Width
SLE	Stressful Life Events
IHHP	Isfahan Healthy Heart Program
PD	Panic Disorder

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.dsx.2019.05.006.

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