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Evaluation of Psychological Stress and its Association with Glycosylated Hemoglobin and C-reactive Protein in Physicians

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ABSTRACT

Throughout the world physicians face stress because of time pressures, workload, multiple roles and emotional issues. As a result, they are prone to develop psychological stress and related health problems. Evaluation of the psychological stress and its association with glycosylated hemoglobin and CRP level in physicians. This cross-sectional study was conducted from January to December, 2022 among70 apparently healthy physicians working in Dhaka Medical college Hospital. The General Health Questionnaire-12 (GHQ-12) was used to evaluate the stress level. Stress was categorized by the scores from GHQ-12. Score '≥4'denoted psychiatric morbidity. The study parameters were stress score, HbA_1C and CRP. Chi-square test, ANOVA followed by post hoc Bonferroni test, Pearson's correlation test was performed as applicable. Results were presented as mean and standard deviation (mean ± SD). Among all study subjects 10% participants had no stress, 27.1% participants had low stress and 62.9% participants had psychiatric morbidity. The mean ±SD of HbA_1C of male and female physicians were 5.20±0.63 and 5.31±0.63 respectively. The mean ±SD of CRP in male and female physicians were 3.89±4.97 and 3.15±3.47 respectively. High stress score showed positive correlation with increased level of glycosylated hemoglobin. In male physicians CRP level showed negligible negative correlation with high stress but it showed positive correlation in female physicians. In male physicians none of the study parameters had statistically significant relationship with stress. In female physicians, high stress score was statistically significant relationship with increased HbA_1C. This study implies that high stress level influences the increase of glycosylated hemoglobin in all physicians. Female subjects were more affected by high stress than males. CRP level had non-significant alteration with high stress score in both genders.

Keywords: Stress, GHQ-12, HPA axis, Glycosylated hemoglobin, HbA_1C, C-reactive protein, and CRP.

INTRODUCTION:

The concept of stress was first introduced in the field of medicine by endocrinologist Dr. Hans Selye. He defined stress as "the non-specific response of body to any demand placed upon it" and provided the theory of stress 'general adaptation syndrome' which includes three stages - alarm, resistance and exhaustion (Armborst *et al.,* 2021, Konduru, 2011). Brain is the primary organ of stress perception and subsequent response. It works via a complex, non-

linear network through the sympathetic and parasympathetic systems, the hypothalamic-pituitary-adrenal (HPA) axis, the immune system, metabolic hormones and molecular processes within all organs to promote adaptation to protect the body.

Nevertheless, exposure to chronic stress leads to an overutilization of these mediators and adaptation to the chronicity can result in persistent dysregulation that contributes to stress-related pathophysiology[2]. many events of daily life that elevate and sustain activities of physiological systems and cause sleep deprivation, overeating, and other health-damaging behaviors, producing the feeling of being 'stressed out' (McEwen 2006).

Hypothalamic-pituitary-adrenal axis

The major stress responsive systems are hypothalamus-pituitary-adrenal (HPA) axis and autonomic nervous system (ANS). The target tissues for the stress system modulation is regulated primarily by the nerve signals and hormones by these systems (Priyadarshini and Aich, 2011). Glucocorticoids (GC), mainly cortisol is the main modulator of stress response. Hypothalamus synthesize and secrete vasopressin and CRH which regulate the pituitary gland and stimulate the production of ACTH which stimulates the adrenal cortex to produce GCs, mainly cortisol. The GCs give negative feedback to hypothalamus and pituitary to suppress the production of CRH and ACTH, thus the negative feedback loop become completed (Konduru, 2011). Stress is the exaggerated systemic biological response of an individual to different kinds of stressors. Hypersecretion of cortisol is a natural adaptive response under stress (Mishra and Pandey, 1995; Al-Shehari *et al.,* 2024).

Activated HPA-axis under stress stimulates release of large amounts of GC. GC stimulates gluconeogenesis and glycogen storage in liver, decreases glucose uptake and utilization in skeletal muscle and white adipose tissue. If the stressor persists for a prolonged period, hypercortisolemia results in insulin resistance, visceral fat accumulation and decreased lean body mass. GC leads these effects by activating numerous genes involved in hepatic glucose metabolism, such as phosphoenol pyruvate carboxykinase and glucose-6-phosphatase. Hepatic gluconeogenesis also increased by glucagon and epinephrine (GC stimulates these hormone secretion). Consequently, GC antagonizes the metabolic effect of insulin by reducing the translocation of GLUT transporter on cell surface (Ingrosso *et al.,* 2021). The effect of ANS on insulin action is both faciliatory and inhibitory. It has both direct neural and indirect hormonal pathway for glucose metabolism. So elevated blood glucose level eventually impairs pancreas's ability to respond to a glucose stimulus. As a result, glucose toxicity occurring from chronic, intermittent, stress-induced elevations in blood glucose produces a permanent effect on pancreatic secretory ability (Surwit *et al.,* 1992). Behavioral changes commonly observed in chronic stress such as sedentary lifestyle, changing of dietary habits leads to weight gain and abnormal glucose metabolism (Konduru, 2011). Psychological stress became one of the significant contributors to baseline inflammation and this affects CRP levels in individuals. In response to the release of inflamematory cytokines, CRP is produced exclusively by hepatic cells and its production is regulated by pro-inflammatory cytokines such as interleukin-1 (IL-1), tumor necrosis factor- (TNF), and especially IL-6 (Tamakoshi *et al.,* 2003, Haque *et al.,* 2020). Some studies suggest, stress may increase C-reactive protein production as it is an important component of innate immunity. In persistent stress this contributes to the progression of CVD by inducing pro-atherosclerotic activities in vascular endothelial cells (Kaur and Kaur, 2018). Unlike other pathological conditions which induce specific responses from the systems they affect, stress induces a generalized response from all systems of the body and each response can also be triggered by other conditions (Johnson *et al.,* 2013).

Stress is known to be associated with increased prevalence of a number of cardio-metabolic diseases as it is partially responsible for disruption in metabolic homeostasis. Psychological stress and unhealthy lifestyle consisting of a poor diet, smoking, sleep disturbances, lack of physical activity have long term health hazards in both adult males and females (Goldman-Mellor *et al.,* 2010).

MATERIALS AND METHODS:

Setting and participants: This cross-sectional study was designed to assess the psychological stress by a questionnaire and then measurement of stress related biomarker changes in blood i.e. HbA_1C and CRP. This was carried out in Dhaka Medical College Hospital from January to December, 2022. Total 70

apparently healthy male (20) and female (50) physicians were selected by purposive sampling technique.

Inclusion and exclusion criteria

Their age was between 30 to 59 years and BMI within the normal range of (18.5-29.9) kg/m^2. Participants of hypertension, diabetes mellitus, chronic inflammatory disease, psychiatric conditions or pregnant were not included in this study.

Procedure

Informed written consent was taken. Detailed personal history, family history, medical history and demographic data were recorded. HbA_1c and CRP were estimated in the department of laboratory medicine of Dhaka Medical College Hospital. 4 ml venous blood was collected, 2 ml whole blood was taken in a test tube containing EDTA anticoagulant for estimation of HbA_1c. The remaining blood was centrifuged for separation of serum. After that, supernatant serum was used for analytical measurement of CRP. HbA_1c was measured by turbidimetric immuoinhibition method and reading was taken by Dimension® Automated Biochemistry Analyzer method. Normal range was considered <5.7%[9]. C-Reactive Protein (CRP) was measured by Extended Range (RCRP) method used on the Dimension® clinical chemistry system. Normal range was considered as 0.01-1.0 mg/dl (Johnson *et al.,* 2013). GHQ-12 is a self-administered screening tool designed to assess mental disturbances for last few weeks. This questionnaire was introduced in 1988 by Goldberg and Williams (Kaur and Kaur, 2018; Sanchez-Lopez and Dresch, 2008). GHQ-12 is considered to be a unidimensional scale of psychological distress, consisting the items capturing symptoms of anxiety, depression, social dysfunction, and loss of confidence. Study members respond using a four-point Likert scale (symptom present: 'not at all' or 'same as usual' scored zero; 'more than usual' or 'much more than usual' scored one point) (Russ *et al.,* 2015).

In this study, the scoring method of bimodal scale (0-0-1-1) was chosen. Score 0 was considered as no stress and score 1-3 was considered as low stress and ≥4 as psychiatric morbidity (Ramirez *et al.,* 1996). Statistical analysis: Statistical analysis was performed by using a computer based statistical program SPSS version 26.0. Chi -square test was done to analyze the categorical data p value of < 0.05 was considered as level of significance. One-way ANOVA followed by Bonferroni test was performed to compare the study parameters in all three categories of stress among study subjects. Pearson's correlation co-efficient test was performed to explore the relationship between stress level and study parameters of the study subjects.

RESULTS:

In this study, almost all participants were in overweight state. Although all female participants were non-smokers, 40% male participants were smokers (**Table 1**). 62.9% participants were experiencing high stress (psychiatric morbidity), presented in **Fig 1**. 40% participants were in pre-diabetic category (**Table 2**).

Table 1: General characteristics of study subjects (n=70).

Parameters	Male (n=20)	Female (n=50)
Age (years)	34.1±4.1	37.9±5.6
Body mass index (kg/m^2)	25.7±3.31	26.8±2.9
Blood pressure (mmHg)		
Systolic BP	122.5±9.1	114.5±11.4
Diastolic BP	81.5±5.9	76.3±9.04
Heart rate (bpm)	80.5±5.4	78.4±6.2
Smoker (%)	8(40.0%)	0 (0%)

Table 2: Frequency distribution of study parameters in study subjects.

HbA_1C	Male (n=20)	Female (n=50)	*p*-value
Normal (<5.7)	12(60.0%)	30(60.0%)	1.000
Pre-diabetic (5.7-6.4)	8(40.0%)	20(40.0%)	
CRP			
Normal (0.01-1.0 mg/L)	10(50.0%)	12(24.0%)	
High (>1mg/L)	10(50.0%)	38(76.0%)	0.097

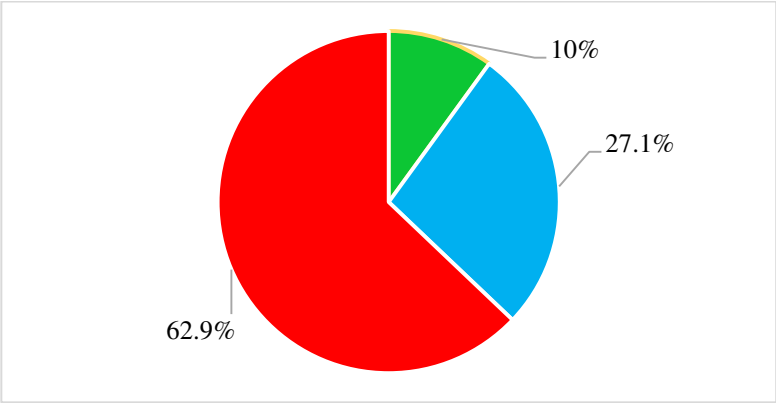

Fig. 1: Distribution of study participants in according to stress score (n=70) (n=total number of study subjects).

Table 3: Level of study parameters in study subjects (n=70).

Parameters	Male (n=20) Mean±SD Range-(max-min)	Female (n=50) Mean±SD Range-(max-min)
HbA1c (%)	5.20±0.63 (4.2-6.2)	5.31±0.63 (4.2-6.4)
CRP (mg/dl) **Median**	3.89±4.97 1.03	3.15±3.47 1.75

Data were expressed as mean±SD. Median was estimated for data in skewed distribution. Values in parentheses indicates range.

In present study, the level of HbA_1c and CRP in different stress categories in male physicians was not significant (**Table 4**) whereas in female physicians' level of HbA_1c varied in different stress categories significantly (**Table 5**). Overall, high stress score showed positive co-relation with increased HbA_1c which was significant as well. Relation between High stress score and CRP level was inconclusive in all aspects although in our study we found that smoker participants had high stress score as well as high CRP level (**Table 7**).

Table 4: Comparison of Stress score with HbA_1C and CRP in male patients (n=20).

Variables	Stress score			*P* value
	No stress (n=2)	Low stress (n=4)	Psychiatric morbidity (n=14)	
HbA_1c	4.80±0.00 (4.8-4.8)	5.10±0.78 (4.5-6.2)	5.28±0.64 (4.2-6.1)	.595
CRP (mg/dl) Median	1.00±0.00 (1.00-1.00)	5.68±7.48 (1.00-16.70)	3.80±4.58 (.20-14.30)	.576

Table 5: Comparison of Stress score with HbA_1C and CRP in female patients (n=50).

Variables	Stress score			*P* value
	No stress (n=5)	Low stress (n=15)	Psychiatric morbidity (n=30)	
HbA_1c	4.80±0.34 (4.3-5.2)	5.13±0.64 (4.2-6.4)	5.49±0.61 (4.3-6.4)	.030*
CRP (mg/dl) **Median**	3.48±3.30 (1.00-8.40)	2.39±2.20 (.50-7.50)	3.55±4.00 (.40-18.70)	.573

Post Hoc Bonferroni Test	*P* value
HbA_1C	

No stress vs Low stress	0.861
No stress vs Psychiatric morbidity	0.046*
Low stress vs Psychiatric morbidity	0.206

One-way ANOVA followed by Bonferroni test was performed to compare HbA_1C level among female physicians in different categories of stress. The test of significance was calculated and using 95% CI for all comparisons, p value < 0.05 was accepted as level of significance. *P* value reached from ANOVA test.

Table 6: Correlation of HbA_1C and CRP with stress score in study subjects.

Variables		**Pearson's**	**Correlation**	
	Male		**Female**	
	r- value	*p*-value	r- value	*p*-value
HbA_1C (%)	+0.378	0.100	+0.339	0.016*
CRP (mg/dl)	-0.068	0.776	+0.177	0.218

Pearson's correlation coefficient test was performed to compare relationship between stress score with the study parameters. *p* value < 0.05 was accepted as level of significance. n=Total number physicians. *=Statistically sign

Table 7: Study parameters of the study subjects between smokers and non-smokers in male physicians (n=20).

Parameters	**Non-smoker (n=12) Mean±SD**	**Smoker (n=08) Mean±SD**	***p*-value**
Stress score	3.92±2.64 (0-10)	5.0±3.58 (0-11)	0.446
HbA1c (%)	4.99±0.59 (4.2-6.1)	5.50±0.59 (4.8-6.2)	0.076
CRP (mg/dl)	2.47±2.46 (0.20-8.0)	6.03±6.9 (1.0-16.7)	0.119

DISCUSSION:

In this study among all physicians (n=70), 27.1% had low stress and 62.9% had psychiatric morbidity; this indicates a high prevalence psychiatric morbidity in physicians. Factors causing psychological stress in physicians can originate from workplace stress, conflict between personal and professional life, heavy expectations, long working hours and corruption in healthcare system. A study by Munir *et al.* (2017) showed that 86.2% doctors were moderately stressful and 11.7% doctors were very stressful who were working in different CMH hospitals. Another study by Haque *et al.* (2020) found high stress (20%) among junior doctors working in 9 different tertiary level hospitals in Dhaka city. Sasidharan *et al.* (2016) conducted a study in a teaching hospital among doctors and found that 44.74 % of them were experiencing different levels of stress. These findings are similar to present study as all these studies indicates high prevalence of stress in tertiary level hospitals in physicians. Sahasrabuddhe *et al.* (2015) conducted a study to measure stress level among resident doctors in a tertiary hospital and found 37.3 % study participants had stress which is similar to present study. Khuwaja *et al.* (2004) conducted a study among male and female doctors in three tertiary care teaching hospitals. About half (48%) of the doctors graded job stress from high to very high levels. Females had higher level of stress than males but this was not statistically significant which is similar to this study.

In our study, the relationship between increased stress score and elevated glycosylated hemoglobin in both male and female physicians were positively correlated. Among male and female physicians 40% were pre-diabetic separately. Female physicians had statistically significant relationship between glycated hemoglobin and higher stress score. Female physicians also had higher mean value of BMI than male physicians (female 26.8±2.9; male 25.7±3.31). Armborst *et al.* (2021) observed positive correlation between chronic perceived stress and increased level of glycated hemoglobin in healthy individuals which is similar to present study. Yamamoto *et al.* (2011) conducted a study and they found association in stress score, BMI and increased

glycated hemoglobin among study subjects which agree with present study. Schuck, (1988); Netterstrom *et al.* (1988) conducted similar type of study on medical students of both genders to see the effect of examination stress on glycosylated hemoglobin. In both studies positive correlation was found between increased stress level and increased glycolsylated hemoglobin which is similar to this study. Sustained psychological stress results in increased levels of glucocorticoids, particularly cortisol in the circulation for a prolonged period. Cortisol causes gluconeogenesis and stimulates release of glucagon, growth hormone; these also increase blood glucose level. Cortisol also antagonizes action of insulin action. All these factors lead to insulin resistance and a constant hyperglycemic state remains in the body.

In this study, among male physicians CRP level was negatively correlated with higher stress score which was not statistically significant. Male smokers had higher mean value of CRP than non-smokers. Though 50% male physicians had higher CRP values than normal, the difference was not statistically significant. Among female physicians, elevated CRP level was positively correlated with higher stress score though it was not statistically significant. Clays and colleagues, (2005) conducted a retrospective analysis, they observed positive correlation but statistically insignificant relation with stress which is similar to this study. Yamamoto *et al.* (2011); Armborst *et al.* (2021) found that stress had a positive correlation with CRP level and increased CRP level is associated with increased stress score and increased BMI which is similar to present study for female physicians. Goldman-Mellor *et al.* (2010) suggested in their study that increased body weight is the main reason for elevation of CRP level in chronically stressed persons as these persons tend to gain excess weight which agrees with our study in cases of female physicians. McDade *et al.* (2006), Poanta *et al.* (2010) found that perceived stress was positively associated with CRP, they also observed that with increased stress level, concentration of CRP increased more in women than in men. This is similar to present study. Chronis psychological state causes baseline inflammation in the body and release of cytokines stimulates production OD CRP from hepatocytes. Increased body weight also contributes to this baseline inflammation. As a result, elevated CRP level is found in stressful conditions.

CONCLUSION:

Our findings from this study indicates that mean stress score was higher in females than males, mean body weight was also increased in females. Among male participants 40% were smokers while in females there was none. As smoking is thought to be one of the coping methods for high stress; it indicates that male physicians cope well with stress than female physicians. We found that, high perceived stress as in higher stress score influences one's body weight and lifestyle which in turn increases HbA_1C level in both male and female physicians. The relation between psychiatric morbidity and HbA_1C was statistically significant in female participants only. Stress score was negatively correlated with CRP in male physicians and positively correlated in female physicians but this finding not conclusive as participants CRP levels were found in skewed distribution. Mean CRP of smokers were much higher than other participants.

Author Contributions

T.M. conceptualization, methodology, writing the manuscript. D.B.; U.S.; S.A.A; and S.F. contributed in data analysis, investigation, supervision, visualization. K.F.; S.H.; F.H.; and T.I.T. finally checked the manuscript and editing, Data Curation, Funding acquisition, and Formal Analysis. All authors who are involved in this research read and approved the manuscript for publication.

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CONFLICTS OF INTEREST:

No conflicts of interest.

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