<u>Original Research Article</u>

Study on the Impact of Chronic Psychological Stress on Clinical Biomarkers and Health-Related Quality of Life in Patients Attending a Tertiary Care Hospital

M. Hithesh Reddy[1], D. Niketan[2], Jayakrishna Murthy[3], R. Shravya[4]

[1]Associate Professor, Department of General Medicine, Viswabharathi Medical College, Penchikalapadu, Kurnool, Andhra Pradesh
[2]Associate Professor, Department of General Medicine, Viswabharathi Medical College, Penchikalapadu, Kurnool, Andhra Pradesh
[3]Assistant Professor, Department of Pediatrics, Viswabharathi Medical College, Penchikalapadu, Kurnool, Andhra Pradesh
[4]Associate Professor, Department of Pediatrics, Viswabharathi Medical College, Penchikalapadu, Kurnool, Andhra Pradesh

Abstract:

Background: Stress due to work either as professionals or students has become common due to changes in the globalized society with its demands, rapid progress in communication, resulting in adverse health conditions of organic and functional nature. The stress related diseases affect all the systems in the body and produce abnormal clinical biomarkers. The most common systems which may lead to morbidity and mortality are Coronary artery disease (CAD). The present study explores the hidden mechanisms playing their role causing the disease and the methods of evaluation which helps to plan therapeutic interventions.

Aim of the Study: To assess the impact of stress on the clinical biomarkers and Health related quality of life in patients attending the General Medicine department.

Materials: Among 156 subjects, there were 107 (68.58%) males and 49 (34.41%) female patients. The mean age was 41.53±6.12. 15 (09.61%) patients were aged between 08 and 15 years. 28 (17.94%) patients were aged between 16 and 25 years. 26 (16.66%) patients were aged between 26 and 35 years. 38 (24.35%) patients were aged between 36 and 45 years. 27 (17.30%) patients were aged between 46 and 55 years. 23 (14.74%) patients were aged between 56 and 65 years. Cortisol levels were of 05 to 15 mcg/dl in 21 (13.46%), 16 to 25 mcg/dl in 38 (24.35%).

Results: CTS2 instrument results revealed 28 (17.94%) patients belonged to category-0, 31 (19.87%) patients belonged to category-1 or 2, 28 (17.94%) patients belonged to category-3, 41 (26.28%) patients belonged to category-4, 12 (07.69%) patients belonged to category- 5, 09 (05.69%) patients belonged to category-6, 07 (04.48%) patients belonged to category-7.

Conclusions: The study concludes that the biomarkers cortisol, Genome sequencing in addition to BMI, age and gender prevalence are consistent with previous studies in predicting the mortality in chronic diseases related pathophysiological changes causing stress related psychiatric and mental problems in the subjects. The mental and physical stress measuring instruments are very useful in assessing the grades of stress and to plan the treatment. The most useful scales are SF-12, CTS2 and revised LCc-R.

Keywords: Stress, Professional, Student, Organic Disease, Functional Disease, And Cardiovascular Diseases.

Introduction

Stress in the life of individuals is perceived in different degrees based on the personality. [1] Stress has a negative impact on the Health related quality of life of such persons and is identified as a major health issue. [2] Stress could be in the form of social factors like poverty, early life experiences, available social supports, employment status, and provision of food sources, transport options and characteristics of the work environment. [3] Certain other authors have taken experience of patients witnessing violent acts involving the family members; particularly intimate life partners, political violence, and mistreatment during childhood; as the stress factors. [4,7] Other authors have included factors as stressful such as war and conflict, natural disasters, academic failure, injury, job loss, major

financial crises, divorce, illness or death of a loved one to the experience of poor health. [8,9] Studies on women by few authors has given a different type stress factors such as home violence, spouse harassment and other social and health related issues like increased sexual and reproductive health problems, chronic pain, somatic conditions, gastro-intestinal disorders, suicidal ideation and risk-taking behaviours affecting the health related quality of their lives (HRQoL) with a negative impact. [10,11,12] Current clinical work on repeated stress associated with childhood adversities, have concluded that the childhood stress may rise the risk of physical and mental illness leading to premature death with or without the continued presence of the stressor. [13] The literature also specifies that such stress on cumulative basis may prevent the body's capabilities to repair its own physiological systems which are deranged, further leading to increased wear and tear. Such dysregulation may lead to pathophysiological responses. [14,15] Another theory in vogue is that such stress could cause prolonged exposure to stress hormones which alter the various physiological systems, including metabolic and inflammatory pathways, and immunological defense systems in the body which can lead to impaired functions and cell senescence. [16,17] A review of literature confirmed that there is a strong and consistent evidence and association between stress factors and the causes and prognosis of CHD. [18] Such an increased risk contributed by these stress factors was of similar order to CHD risk factors such as smoking, dyslipidemia and hypertension. [19] In this context the present study was conducted to assess the impact of stress on the clinical biomarkers and Health related quality of life in patients attending the General Medicine department.

Materials:

Type of Study: A cross sectional study.

Institution of study: Viswabharathi Medical College and Hospital, Kurnool.

Year of Study: January 2022 to December 2024.

Study populations involved 156 subjects attending the department of General Medicine with various organic and functional diseases related to different systems of the body with evidence of stress being common to all. An ethics committee of the institute approved the study and committee approved consent form and proforma were used. Inclusion Criteria: Subjects aged from 08 years to 65 years were included. Subjects residing in the same geographic area were included. Subjects with diseases involving all the systems of the body were included. Subjects with all the types of functional diseases were included. Subjects with complaints of disturbed quality of life were included. Exclusion Criteria: Subjects aged below 08 years

and above 65 years were excluded. Subjects with immune-compromised diseases were excluded. Subjects not willing to participate in the study were excluded. Patients with habits of smoking, caffeine and alcohol were excluded. Subjects with disturbances of sleep were excluded. Subjects with regular exercise habits were excluded. Subjects without the life stressors were excluded. All the patients were subjected to collection of data which was classified as: Type and chronicity of Stressful life events (SLEs) from a structured questionnaire:

The questionnaire included two types of measures: 1. The Life Stressor Checklist – Revised (LSC-R) and 2. [11] And the Revised Conflict Tactics Scale (CTS2), [20]. The former (LSC-R) had a 30 item questionnaire used to assess events in a person's life that were found frightening or upsetting like natural disasters, sexual or physical assault and illness or death of a relative [11] and also included items more unique to women like miscarriage and abortion, or being unwillingly separated from children. The age at which the subjects experienced the SLEs was noted, the age at which the event occurred and the impact of the SLE now for the past 12 months. The subject is asked to give the age when the event started and they believe that they were in harm in terms of "yes" or "No. The effect of the event was rated on a five-point intensity scale (1 = "not at all or never" to 5 = "extremely").

Respondents are asked to identify the three events that currently have the greatest impact on them. The CTS2 instrument was used to assess the aggression and conflict within intimate relationships of their close associates. The instrument consisted of 39 items assessing both perpetration of violence and also victimization. The response options had 8 choices (Categories 1-7 and 0). The answer for Category 1 or 2 is taken as the similar number of times the stress event occurred; once or twice in the past year.

For Categories 3 to 5, the midpoint of the category is coded. (For example: Category 3 (3-5 times) is coded as 4, Category 4 (6-10 times) is coded as 8, and Category 5 (11-20 times) is coded as 15. Category 6 (More than 20 times) should be coded as 25. Category 7 is given a score of 0 if scores for the previous year do not reflect abuse or conflict. All the subjects were tested for self-extracted buccal swab. Genomic DNA was extracted from buccal swabs within 48 hours of collection. DNA integrity and concentration in each sample was analyzed. Primer sequences (5'to 3') were: tel2b, GGCTTGCCTTACCCTTACCCTTACCCTTACC CTTACCCT; tel1b, CGGTTTGTTTGGGTTTGGGTTTGGGTTTGGG TTTGGGTT; hbg2: ACCAACTTC ATCCACGTTCACC and hbg1, GCTTCTGACAC AACTGTGTTCACTAGC. The Health related

quality of life was assessed by using two scales. One is the Medical Outcomes Study Short Form 12 (SF-12®), a widely used measure of health-related quality of life. [24] The scores are expressed as: PCS-12: Physical score: 55.25 and Mental score-12 60.69. (Both taken as two summary scores are reported from the SF-12 – a mental component score (MCS-12) and a physical component score (PCS-12). The scores may be reported as Z-scores (difference compared to the population average, measured in standard deviations). The United States population average PCS-12 and MCS-12 are both 50 points. The United States population standard deviation is 10 points. So each 10 increment of 10 points above or below 50 corresponds to one standard deviation away from the average.

The other is the Center for Epidemiologic Studies Depression Scale (CES-D), a 20-item instrument that examines recent depressed mood or affect. [21] The scores are calculated by the total score is calculated by finding the sum of 20 items. Scores range from 0-60. A score equal to or above 16 indicates a person at risk for clinical depression. Other variable observed in the subjects during the study were body mass index [22], physical activity [26,23], alcohol and tobacco use [24], fruit and vegetable consumption [25], and sleep disturbance [26]. Serology tests were performed on all the subjects to include serum Cortisol levels. Relative telomere length assay by quantitative polymerase chain reaction (PCR) Relative telomere length assay by quantitative polymerase chain reaction (PCR) was conducted in all the patients. All PCRs were performed on the ABI 7500 Fast Real-Time PCR System (Applied Biosystems).

Statistical analysis: All statistical data will be analysed using SPSS version 19.0 and AMOS version 19.0 statistical packages. [24] The demographic characteristics of the sample will be reported as means, and standard deviations for continuous variables, and frequencies and percentages for categorical variables. Descriptive exploration of the main independent variable will determine the frequency of occurrence, percentage, and rank order of each type of SLEs; the total number of SLEs exposures will then be calculated by summing the number of affirmative responses given on the LSC-R for each participant.

Results

The demographic data of the 156 subjects was tabulated in the Table 1. There were 107 (68.58%) males and 49 (34.41%) female patients. The mean age was 41.53±6.12. 15 (09.61%) patients were aged between 08 and 15 years. 28 (17.94%) patients were aged between 16 and 25 years. 26 (16.66%) patients were aged between 26 and 35 years. 38 (24.35%) patients were aged between 36 and 45 years. 27 (17.30%) patients were aged between 46 and 55 years. 23 (14.74%) patients were aged between 56 and 65 years. (Table 1) BMI between 10 and 15 was observed in 27 (17.30%) patients. BMI between 10 and 15 was observed in 27 (17.30%) patients. BMI between 16 and 25 was observed in 91 (58.33%) patients. BMI between 26 and 35 (%) was observed in 38 (24.35%) patients. 102 (65.38%) patients had no habit of physical exercise. 54 (34.61%) patients had the habit of physical exercise. Alcohol consumption was present regularly in 38 (24.35%) patients. Smoking habit was observed in 29 (18.58%) patients and no smoking habit observed in 127 (81.41%) patients. Sleep disturbances were noted in 63 (40.38%) patients and no sleep disturbances were noted in 93 (59.61%) patients. (Table 1)

Table 1: Showing the demographic data of the subjects (n-156).

Variable	Number	Percentage	P value
Age			
08 to 15	**15**	**09.61**	
16 to 25	**28**	**17.94**	
26 to 35	**26**	**16.66**	**0.001**
36 to 45	**38**	**24.35**	
46 to 55	**27**	**17.30**	
56 to 65	**23**	**14.74**	
Gender			
Male	**107**	**68.58**	
Female	**049**	**31.41**	**0.001**
BMI			
10 to 15	**27**	**17.30**	
16 to 25	**91**	**58.33**	**0.001**
26 to 35	**38**	**24.35**	
Physical activity			**0.124**
Yes	**054**	**34.61**	
No	**102**	**65.38**	
Alcohol			**0.324**

Yes	038	24.35	
No	118	75.64	
Smoking			0.221
Yes	029	18.58	
No	127	81.41	
Vegetable consumption			0.311
Yes	57	36.53	
No	99	63.46	
Sleep disturbances			0.147
Yes	63	40.38	
No	93	59.61	

Serum cortisol levels and genome sequencing of the buccal epithelium were estimated in all the subjects and it showed the values which were tabulated in Table 2. Normal range values taken were 05 to 25mcg/dl. Normal values of 05 to 15 mcg/dl were noted in 21 913.46%) of the patients, cortisol levels of 16 to 25 mcg/dl were noted in 38 (24.35%) of the patients. Abnormal values between 26 and above 35 were noted in 97 (62.17%) patients. (Table -2) Genomic sequencing was done using buccal mucosa and observed that tel2b: sequence was noted in 31 (19.87%) patients, tel1b sequence was noted in 29 (18.58%) patients, hbg2 sequence was noted in 61 (39.10%) patients and hbg1 sequence was noted in 35 (22.43%) patients. (Table 2) CES scores were 0 to 06 in 11 (07.05%) of the patients.

Table 2: Showing the biological markers used in the study and their prevalence (n-156)

Biological markers	Number	Percentage	P value
Serum Cortisol levels in mcg/dl			
05 to 15	21	13.46	
16 to 25	38	24.35	
26 to 35	58	37.17	
35 and above	39	25	0.001
Genomic sequencing			
tel2b:(GGCTTGCCTTACCCTTACCCTTACCCTTACCCTTACCCT)	31	19.87	
tel1b:(CGGTTTGTTTGGGTTTGGGTTTGGGTTTGGGTTTGGGTT)	29	18.58	
hbg2: (CACCAACTTCATCCACGTTCACC)	61	39.10	0.001
hbg1: (GCTTCTGACACAACTGTGTTCACTAGC)	35	22.43	

The mean age at which an event stressful in the life of the subjects occurred was 13.50±2.50 years. 40 (25.64%) patients replied that it has no effect on their life. 18 (11.53%) replied that occasionally it affects their mood. 31 (19.87%) of the patients regularly the event affects their lives. 22 (14.10%) patients suffered from regularly moderate degree of anxiety. 44 (28.20%) of the patients revealed extreme psychiatric depressions due to the event. (Table 2) CTS2 instrument results revealed 28 (17.94%) patients belonged to category-0, 31 (19.87%) patients belonged to category-1 or 2, 28 (17.94%) patients belonged to category-3, 41 (26.28%) patients belonged to category-4, 12 (07.69%) patients belonged to category- 5, 09 (05.69%) patients belonged to category-6, 07 (04.48%) patients belonged to category-7. (Table 2) Among the HRQoL scales used SF-12 showed Physical component score 0 to 20 in 36 (23.07%) patients, 21 to 40 in 58 (37.17%) patients, 21 to 40 in 52 (39.74%) patients. Similarly Mental component score was 0 to 20 in 27 (17.30%) patients, 21 to 40 in 44 (28.20%) patients, 41 to 60 in 80 (51.28%) patients. The CES scores were 0 to 16 in 11 (07.05%) patients, 17 to 26 in 35 (22.43%) patients, 27 to 36 in 74 (47.43%), 37 to 46 in 24 (15.38%) and 47 to 56 percent in 02 (01.48%) of the patients. (Table 2)

Table 3: Showing the Stressful life events scales and HRQoL scales and their results in the subjects of the study (n-156)

Scales used to measure the effects of stress	Number	Percentage	P value
SLE scales			
1. Revised (LSC-R)			
Mean age when the event started in Yrs	13.50±2.50	--	
Whether the event affecting presently			
Scale			
1. Not at All	40	25.64	0.001

2 Occasional	**18**	**11.53**	
3 Regular but mild	**31**	**19.87**	
4 Regular but moderate	**22**	**14.10**	
5 Extremely affecting	**44**	**28.20**	
2. CTS2 instrument			
Category- 0	**28**	**17.94**	
Category 1 or 2- 1 or 2 times the stress event occurred; once or twice in the past year.	**31**	**19.87**	
Categories 3- (3-5 times) are coded as 4; - the midpoint of the category is coded.	**28**	**17.94**	
Category 4- (6-10 times) is coded as 8,	**41**	**26.28**	
Category 5- (11-20 times) is coded as 15.	**12**	**07.69**	
Category 6 (More than 20 times) should be coded as 25.	**09**	**05.76**	
Category 7 is given a score of 0 if scores for the previous year do not reflect abuse or conflict.	**07**	**04.48**	
HRQoL scales **1. SF-12** **Physical Component score**			
00-20	**36**	**23.07**	
21-40	**58**	**37.17**	
41-50	**62**	**39.74**	**0.001**
Mental Component score			
00-20	**27**	**17.30**	
21-40	**44**	**28.20**	
41-50	**85**	**51.28%**	
2. CES			
00-16	**11**	**07.05**	
17-26	**35**	**22.43**	
27-36	**74**	**47.43**	
37-46	**24**	**15.38**	
47-56	**02**	**01.28**	

Discussion:

The present study was an attempt to address the impact of physiological stress caused by various diseases on the physical and mental abilities in patients attending a tertiary rural Hospital and its effect on the clinical biomarkers and Health related quality of life. The aim of the study was ultimately to understand the processes of prolonged exposure to pathophysiological stress of the diseases. This attempt helped us to understand the relation between the stress and the changing biomarker values and Stress related physical and mental scoring and Health related quality of life score. Further such data would help us to understand the factors which contribute to poor health in the subjects and help us to improve the evidence base recommendations for gaining total health and reduce future chronic health problems. Normal range values taken were 05 to 25mcg/dl. Normal values of 05 to 15 mcg/dl were noted in 21 913.46%) of the patients, cortisol levels of 16 to 25 mcg/dl were noted in 38 (24.35%) of the patients. Abnormal values between 26 and above 35 were noted in 97 (62.17%) patients. (Table -2) Usually the cortisol levels of urine, saliva, and blood are used to estimate the significance. But these have limitations. [27] Amongst all he estimation of

cortisol from hair is found to be more accurate. According to Kimberly *et al*, observed that the potential biomarker stress is cortisol from hair rather than samples from urine or salivary samples. They observed that it provides reliable information about the HPA-axis activity reflecting total cortisol release. [28] Besides, it may be useful for the early detection of depression. [29] Genomic sequencing was done using buccal mucosa and observed that tel2b: sequence was noted in 31 (19.87%) patients, tel1b sequence was noted in 29 (18.58%) patients, hbg2 sequence was noted in 61 (39.10%) patients and hbg1 sequence was noted in 35 (22.43%) patients. (Table 2) Elliott AM, Adam S et al [30] from their study concluded that the ACMG variant classification alone is insufficient to diagnose a genetic disease.

The genetic variant should be identified by GWS and categorized by the ACMG guidelines and should be interpreted in term of subject's complete medical history, disease course, family history, physical examination findings, specialist consultations, imaging studies, and other laboratory test results. Only proving that an ACMG pathogenic or likely pathogenic variant does not necessarily confirm the variant is causing an affected individual's genetic disease. [27] CTS2

instrument results revealed 28 (17.94%) patients belonged to category-0, 31 (19.87%) patients belonged to category-1 or 2, 28 (17.94%) patients belonged to category-3, 41 (26.28%) patients belonged to category-4, 12 (07.69%) patients belonged to category- 5, 09 (05.69%) patients belonged to category-6, 07 (04.48%) patients belonged to category-7. (Table 2) CTS2 instrument has been used in evidence-based initiatives to inform IPV treatment and policy by Dixon & Graham-Kevan, in 2011, in therapy to assist disclosure by O'Leary & Murphy, in 1992, and in correctional settings to monitor behavior and treatment progress by Straus, 1993. CTS2 scales were also used in diverse cultural backgrounds, including African Americans and Hispanic Americans, in over 20 different countries by Straus et al., 1996.

In this study Among the HRQoL scales used SF-12 showed Physical component score 0 to 20 in 36 (23.07%) patients, 21 to 40 in 58 (37.17%) patients, 21 to 40 in 52 (39.74%) patients. Similarly Mental component score was 0 to 20 in 27 (17.30%) patients, 21 to 40 in 44 (28.20%) patients, 41 to 60 in 80 (51.28%) patients. The CES scores were 0 to 16 in 11 (07.05%) patients, 17 to 26 in 35 (22.43%) patients, 27 to 36 in 74 (47.43%), 37 to 46 in 24 (15.38%) and 47 to 56 percent in 02 (01.48%) of the patients. (Table 2) Previously, Cheak-Zamora et al. [31] reported the test-retest reliability for SF-12 in a gap of one year as 0.78 for PCS and 0.60 for MCS. The present study interprets the correlation between the annual assessments was that the subjects were clinically ill but relatively stable during the study period. The explanation was consistent with other studies in the literature. [32]

Conclusions

The study concludes that the biomarkers cortisol, Genome sequencing in addition to BMI, age and gender prevalence are consistent with previous studies in predicting the mortality in chronic diseases related pathophysiological changes causing stress related psychiatric and mental problems in the subjects. The mental and physical stress measuring instruments are very useful in assessing the grades of stress and to plan the treatment. The most useful scales are SF-12, CTS2 and revised LCc-R.y ly reported correlations in various populations, the SF-12v2® gives stable correlations in a previously unstudied Medicaid population with a combination of physical and behavioral conditions or SMI.

The results encourage using the SF-12v2® to assess HRQOL in such cohorts with chronic health conditions. The reliabilities of individual scales as well as the summary scores of SF-12 can be used to estimate the variability and covariance structure of the measures when estimating power or sample size for future studies [22]. Moreover, the modestly attenuated correlations in participants with combined physical and mental or behavioral conditions compared to that in the general population need to be considered in future study planning.

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