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A biochemical study of chronic stress and chronic inflammation fibromyalgia

Abstract

Stress is a physical, mental, or emotional agent that induces bodily or psychological tension. Stresses can be external to the environment, psychological, or social conditions or internal illness, or from a medical procedure. There is increasing evidence that stress and depression may play a significant role in the etiology and pathophysiology of fibromyalgia (FM). FM is a syndrome marked by medically unexplained, widespread musculoskeletal pain, hyperalgesia and allodynia, physical and mental fatigue and effort intolerance, non-restorative sleep, mood disturbance and other functions such as gastrointestinal complaints. The goal of the study was to study a relation between external stress, lifestyle, Fibromyalgia and biological profile for 50 females (22-58 years old) Egyptian population. The different methods are used to collect data including Stress sign and Fibromyalgia questionnaire, Body mass index (BMI). Participants underwent a comprehensive series of biochemical laboratory, scan and physical, analysis evaluation such as the biological profile of Standard Health Test Panel, inflammatory, rheumatoid arthritis parameters, autoimmune systemic lupus erythematosus (SLE) and, Gene Mutation (FMF). All studied subject showed normal biological profile and Standard Health Test Panel routine labs as well as normal standard scan. Also, x-rays showing no fractures or other medical problem as compared to the reference range. There is a significant relationship between chronic external stress, fibromyalgia, inflammatory parameters and constant chronic pain. The present explanation is chronic accumulation stress led to FM and autoimmune disease.

Keywords: biochemical data, biological profile, chronic pain, fibromyalgia, inflammation, stress

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Introduction

Stress is any challenge that confuses the body's natural homeostatic mechanisms.[1,2] This challenge may come in the form of a physical stressor or a psychological stressor. Some stress can be beneficial; the pressure it exerts can be an inspiration to achieve necessary goals. But when stress approaches chronic, harmful levels and deleterious consequences develop, from yielded immune function to developmental impairment.[2,3] Chronic stress has been connected with both the hypothalamic–pituitary–adrenal axis (HPA) hyperactivity and HPA axis hypoactivity.[4–6] Alternatively, the association of stress and HPA axis hypoactivity in conditions such as fibromyalgia or rheumatoid arthritis has been used to explain the variation in studies regarding the nature of the HPA axis in chronic stress states.[4–6] The strength of the stress response is primarily governed by glucocorticoids, the primary molecules required in the stress response. Stress can be transient and beneficial, or it can be long-lasting chronic and harmful, that accumulated stress causing suffocation, depression, and paralysis, and constant chronic pain, such as fibromyalgia.[1–6] Fibromyalgia (FM) is a clinical existence characterized by chronic pain lasting more than three months, the proximity of 11 out of 18 hypersensitive points incorporated as trigger points, and diffuse pain, these points, and the clinical mark may be increased gradually during the age. It is more widespread among females and is associated with insomnia, fatigue, gastrointestinal, psychological stress and other. The predominance of depression varies from 49% to 80% in FM. Anxiety and depression worsen social and emotional functionality and the quality of life of patients with FM.[7–9] The present study design to evaluate the relationship between stress, FM, and chronic pain. The assessment through measure Stress sign and Fibromyalgia questionnaire, Body mass index (BMI), scan, physical and laboratory evaluation such as the biological profile of Standard Health Test Panel and inflammatory parameters in 50 females.

Subjects and methods

Subjects characteristics

A total of 50 adult's volunteer females Egyptian included in this study (including the author). All subjects were recruited from period (2003-2018). Inclusion criteria were an age 20-58 year, and a body mass index ranged from 20 to 28kg/m^2 while reference controls required having a BMI 18.5–25kg/m^2 [avoid female with obesity to avert the relation between stress and obesity]. Non-Egyptians, pregnant women and children excluded. The studies were done according to Helsinki Declaration. The patients suffer from pain and stiffness in one or more joints. Also, patients complain of other symptoms that increased gradually during the age as in the next list:

a. They report having difficulty sleeping and feeling fatigued and stiff in the mornings.

b. They noticed problems with cognitive issues such as concentrating and the pain has impacted performing daily activities including cooking, cleaning, and working as a receptionist. They always hope to pass work and regular movements with less pain.

c. They complained of pain in their middle thorax and spine, neck, and lower extremities.

d. They have Diarrhea or constipation or both with pain.

e. They have hypotension and ear pain, headache.

f. They complain of having night sweating, feeling cold or heat or both.

g. They have anxiety and complain of acceleration and slow heartbeat

h. They have Skin sensitive to a temperature low or high.

i. They have no history of significant alcohol or recreational drug use.

j. Some of the subjects have unexplained lactation from the breast.

Patients seek for evaluation of previous complaints and persistent weakness, fatigue, pain, and headaches and other. Groups of the physician have evaluated them, Consultant of liver diseases and digestive system, Orthopedic disorders, and Doctor of Rheumatology, Doctor of Obstetrics, Dr. ENT, Neurology and others. They ask for doing scans and biochemical analysis (The Standard Health Panel and others). The doctors recommended routine labs, x-rays, and scans that were showing no fractures or any abnormality. The lab values (CBC, CMP, erythrocyte sedimentation rate) were all normal. Measure bone density using the X-ray absorption measurement is typical. MRI for Bone, joint, brain and pituitary are normal. Only some inflammatory parameter and autoimmune analysis lab are abnormal. Also, there are anxiety and disorder of heart rhythm (acceleration and slow heartbeat). A lot of checkup by doctors in medicine, a differential diagnosis to distinguishing of a particular disease or condition from others that present similar clinical features know the cause of the symptoms. FM diagnosis by exclusion of diseases that could cause symptoms of the patient complaints. Exclusion of other diseases makes FM diagnosis.[9] In a clinical trial, the exclusion criteria are those characteristics that exclude considered subjects from inclusion in the study. Exclusion criteria may involve factors such as age, sex, race, ethnicity, variety, and stage of disease, the subject's previous treatment history, and the appearance or lack (as in the case of the "healthy" or "control" case) of other medical, psychosocial, or emotional situations. In this study, we do a group of tests to excluded any disease that could overlap with FM. FM has specific characters and also patient ask to do a group of analysis to eliminate other illnesses which may match with the FM symptoms. The American College of Rheumatology has provided classification criteria for fibromyalgia. However, these criteria are not indicated to be accepted for diagnosis. Characteristics incorporate widespread pain including both sides of the body, above and below the waist and the axial skeletal, for at three months. The presence of 11 tender points among the nine pairs of specified sites (18 points). Routine blood testing can help to exclude[9] other differential diagnoses [for example Clinical features show that FM and familial Mediterranean fever (FMF) have some overlapping symptoms, so we do PCR for Familial Mediterranean Fever Gene Mutation (FMF) to an excluded patient with FMF. And Antinuclear Antibody (ANA) to avoid overlapping autoimmune disorders that affect many tissues and organs throughout the body (systemic) such as systemic lupus erythematosus (SLE) with FM. Rheumatoid factor, Anti-cyclic citrullinated peptide to avoid overlapping with rheumatoid arthritis with FM. Thyroid parameters analysis to avoid overlap with a thyroid problem with FM. And so on.

Methods

Body mass index (BMI)

The subjects' weights and heights were measured on a single calibrated scale (SR Scales, SR Instruments). Height and weight were measured using standardized conventional methods. The formula calculated body mass index (BMI): weight in kilograms (kg) divided by height in square meters (m^2). Other data collected included self-reported medical history and blood pressure.[10,11]

Fibromyalgia impact (FIQ) questionnaire

The FIQ has scored in such a way that a higher score registers a more significant impact of the syndrome (FM) on the person. The maximum achievable score of FM is 100. The average FM patient scores concerning 50, severely troubled patients are frequently 70 plus.[12,13]

Sample of the question:

Pain measures

In the past three months:

a) Have you possessed pain in muscles, bones, or joints, last at least one week?

b) Have you had pain in your shoulders, arms, or hands? On which side? Right, left, or both?

c) Have you possessed pain in your legs or feet? On which side? Right, left, or both?

d) Have you maintained the strain or pain in your neck, chest or back?

Fatigue criteria

e) Over the past three months, do you often feel tired or fatigued?

f) Does tiredness or fatigue significantly limit your activities?

Stress impact questionnaire

No single question of questionnaire proves how subjects are experiencing stress, but by looking at the results of groups of items about (physical indicators, sleep indicators, behavioral indicators emotional indicators, personal habits), it may be possible to determine what areas of the life stress affect the most. The score is calculated after defining the fields by the figure the circled numbers in each part and mark the point total for each section. The questionnaire will show how stress affects different parts of subject life, started from very low to danger.[14–16]

Laboratory investigations

Blood was withdrawn after an overnight fast (>9 hours). Biochemical analysis (The Standard Health Panel) were estimated using commercially available kits by Roche/Hitachi Cobas e 601 analyzer (Roche Diagnostics, Mannheim, Germany) utilizing electrochemiluminescence immunoassay and Roche/Hitachi Cobas c 501 analyzer (Roche Diagnostics, Mannheim, Germany) and ELISA.[10,11] Familial Mediterranean Fever Gene Mutation (FMF) was measure by PCR.[17] Autoimmunity Tests (Amyloid A protein, ASO (Nephelometric quantitative), Rheumatoid factor (Nephelometric quantitative, C-reactive protein (Nephlometric quantitative) by Roche/Hitachi Cobas c 501 analyzer (Roche Diagnostics, Mannheim, Germany) and Antinuclear Antibody (ANA)[titre by ELISA], Anti-cyclic citrullinated peptide (anti-CCP) and Calprotectin in Stool by ELISA. Erythrocyte sedimentation rate (ESR) by VES Matic.[18] Microbial Ag-Ab Tests (Bacteria), Widal test by slide method[19] and H-pylori (Ag) according to.[20]

Statistic

Data were fed into the computer using IBM SPSS software package version 20.0. Quantitative data were recorded by mean and standard deviation. For normally distributed data, comparisons between before and after treatment were done using paired t-test. The significance of the obtained results was analyses at the 5% level.[10,11]

Results

The general characteristics of enrolled 50 females (age 20-58 years) where the date expressed using Mean±SD. BMI inclusion criteria show 26.98±6.14 kg/m^2 while normal range should be 18.5 to 24.9. SBP (mmHg) showed 90±4.3, and DBP (mmHg) showed 60±5.1 while the reference range should be Systolic/diastolic=120/80. Fibromyalgia questionnaire score was 82.5±4.61 while the maximum achievable score of FM is 100. The average FM patient scores concerning 50, severely troubled patients are frequently 70 plus. Table 1 represented the stress questionnaire in all subjects that showed the danger score of stress through calculation (physical indicators 65±6.02, sleep indicators 18±5.02, behavioral indicators 50±1.02, emotional indicators 55±4.02, and personal habits 32±3.02.

Table 2 showed the symptoms percent that present in associated with FM in the present subject's studies. The Lower back pain symptoms showed 76% at p<0.001 while Lower back left hip and leg symptoms showed 82.3% at p<0.002. 55 percent of people reported restless leg symptoms at p<0.001. Frequent headaches and general weakness symptoms showed 64.3 and 44.3 5 % respectively at p<0.001. On other hand Joints, pain showed 61.6% at p<0.024. Muscle spasm, Tingling, Balance problems showed 45.3, 42.3, 45% respectively at p<0.001. Also, Irritable bowel syndromes, Chronic fatigue, Bloating symptoms showed 65, 44, 65 % respectively at p<0.001. Also, Depression and Anxiety and disorder of heart rhythm showed 45 and 44% respectively at p<0.001. On the other hand, Sinus problem, Tooth problem (tooth sensitivity), Bladder problems, Rashes and skin sensitivity and Painful menstrual period showed 38, 37, 36, 36, 38 % respectively at p<0.001. Tinnitus (ringing in the ears) or itching or other hearing problems showed 36 at p<0.001. Bladder problem or urgent and frequent urination showed 33% at p<0.001. Jaw pain thorax and spine, neck and Pain and itching in the throat showed 37, 55, 33% at p<0.001 respectively. Night sweating, feeling cold or heat or both showed 55% at p<0.001. Trouble falling asleep and awake feeling tired 66% at p<0.001. Stomach quivers or feels upset showed 46% at p<0.001.

Table 1 Stress questionnaire in total Subject characteristics. Inclusion criteria, FM and stress questionnaires in total Subject characteristics (n=50)

	Subject stress levels (number of subject 50)	Stander score measure personal stress levels[14-16]]				
	Mean±SD	Very Low	Medium	High	Very High	Danger
Physical Indicators Point Total	65±6.02*	22	30	38	48	54+
Sleep Indicators Point Total	18±5.02*	5	8	10	12	14+
Behavior Indicators Point Total	50±1.02*	18	27	36	45	50+
Emotional Indicators Point Total	55±4.02*	21	29	37	46	55+
Personal Habits Point Total	32±3.02*	9	15	20	25	30+

Data was expressed using Mean±SD *: Statistically significant at p≤0.05

Table 2 Fibromyalgia chronic symptoms in total Subject characteristics (n=50)

Symptoms	Percentage of people who reported these symptoms (%)
Lower back pain	76*
Lower back left hip and leg	82.3*
Restless leg	55*
Frequent headaches	64.3*
General weakness	44.3*
Joints pain	61.6*
Muscle spasm	45.3*
Tingling	42.3*
Balance problems	45*
Irritable bowel syndromes	65*
Chronic fatigue	44*
Bloating	65*

Citation: Hamouda AF. A biochemical study of chronic stress and chronic inflammation fibromyalgia. *Pharm Pharmacol Int J.* 2018;6(3):234–243. DOI: 10.15406/ppij.2018.06.00181

Table Continued

Symptoms	Percentage of people who reported these symptoms (%)
Depression	45*
Anxiety and disorder of heart rhythm	44*
Sinus problem	38*
Tooth problem (tooth sensitivity)	37*
Bladder problems	36*
Rashes and skin sensitivity	36*
Painful menstrual period	38*
Tinnitus (ringing in the ears) or itching or other hearing problems	36*
Jaw pain	37*
Bladder problem or urgent and frequent urination	33*
thorax and spine, neck	55*
Night sweating, feeling cold or heat or both	55*
Pain and itching in the throat	33*
Stomach quivers or feels upset	46*
Trouble falling asleep and awake feeling tired	66*

*: Statistically significant at p≤0.05

Table 3 showed the result of biological profile of 50 subjects represented as Mean±SD compared by normal range. PCR for Familial Mediterranean Fever Gene Mutation (FMF) was negative, and the result is confirmed twice as compared to reference report. Virus's profile (HCV-Ab, HBs-Ag, HIV-Ab) and Blood-Syphilis-VDRI then TPHA showed the negative result. Autoimmunity Tests included ASO (Nephelometric quantitative and Rheumatoid factor (Nephelometric quantitative) showed Negative 29±7.11U/ml, and Negative, 4.1±11.03IU/ml, respectively as compared to reference range at p≤0.05. While Autoimmunity Tests included Calprotectin (In Stool), Amyloid A protein and C-reactive protein showed Positive 72±3.22 mg/kg, Positive 89.8±10.02mg/l and Positive 9±5.52mg/l respectively as compared to a standard range at p≤0.05. CBC and Erythrocyte sedimentation rate (ESR) showed normal range as compared to a reference range. Food allergy test (Total IgE) showed normal result 23±12.24U/ml as compared to reference range at p≤0.05. Vitamin D showed normal value as compared to reference range 32±15.03ng/ml. Also, Calcium (total) showed normal range 9.1±16mg/dl as compared to the reference range. Hormones including prolactin (23.6±9.88ng/ml) and thyroid profile T3, T4, TSH showed (1.23±10.34ng/ml, 8.1±5.28µg/dl, 3.1± 4.99µIU/ml normal result respectively as compared to reference range at p≤ 0.05. Microbial Ag-Ab Tests (Bacteria) including Widal test and H-pylori (Ag) showed the normal result as compare to reference range. Lipid, Liver, Renal, Cardiac, Diabetes profiles showed the normal results as compared to reference range at p≤0.05. Furthermore, complete urine and stool analysis showed also normal result as compared to the reference range.

Table 3 Biological profile in total Subject characteristics (n=50)

Test	Result	Normal Range
Serum analysis (number of subject 50)		
Genetic Mutations		
PCR for Familial Mediterranean Fever Gene Mutation (FMF)	Negative	Negative
Viruses		
HCV-Ab	Negative	Negative
HBs-Ag	Negative	Negative
HIV-Ab	Negative	Negative
Blood-Syphilis-VDRI then TPHA	Negative	Negative
Autoimmunity Tests		
Calprotectin (In Stool)	Positive 72±3.22*	Negative Up To 50mg/kg
Amyloid A protein	Positive 89.8±10.02*	Up To 6.8mg/l

Citation: Hamouda AF. A biochemical study of chronic stress and chronic inflammation fibromyalgia. *Pharm Pharmacol Int J.* 2018;6(3):234–243. DOI: 10.15406/ppij.2018.06.00181

Table Continued

Test	Result	Normal Range
ASO (Nephelometric quantitative)	Negative 29±7.11	Negative Less than 200U/ml
Rheumatoid factor (Nephelometric quantitative)	Negative 4.1±11.03	Negative Up To 15IU/ml
Anti-cyclic citrullinated peptide (Anti-CCP)	Negative 10.6±19.02	Negative Up To 20U/ml
Antinuclear Antibody (ANA)[titre by ELISA]	Negative 8.1±14.0	Negative Up To 14U/ml
C-reactive protein (Nephlometric quantitative)	9±5.52*	Negative: less than 3mg/l
Other		
CBC	Normal	See Report
Erythrocyte sedimentation rate (ESR)	Normal	
Vitamin D	32±15.03	6.23–49.9ng/ml.
Calcium(total)	9.1±16	8.1–10.4mg/dl.
Food allergy test		
Total IgE	23±12.24*	Up to 100U/ml
Fertility Related Hormones		
Prolactin (PRL)	23.6±9.88*	3.9–29.5ng/ml
Thyroid Related Hormones		
T3	1.23±10.34*	0.8–2ng/ml
T4	8.1±5.28*	4.7–13.5µg/dl
TSH	3.1±4.99*	0.27–4.2µIU/ml
Microbial Ag-Ab Tests (Bacteria)		
Widal test	Negative	Negative
H-pylori (Ag)	Negative	Negative
Lipid profile		
TG	99±1.89*	Up to 200mg/dl
LDL	75±4.41*	Up to 140mg/dl
HDL	65±9.29*	More than 35mg/dl
CHOLESTEROL	147±7.13*	Up to 200mg/dl
Liver Profile		
SGPT	11±1.22*	Up To 32U/l
SGOT	12±3.29*	Up To 33U/l
Bilirubin total	0.57±3.62*	Up To 1mg/dl
Albumin	3.4±2.85*	3.5–5.4gm/dl
Renal Profile		
Uric Acid	3.6±1.29*	2–6mg/dl
Urea	21±1.86*	10–50mg/dl
Creatinine	0.62±3.52	0.5–0.9mg/dl
Cardiac Profile		
CKMB	0.43±7.12*	Up To 7.2ng/ml
Troponin-T (High sensitive)	6.1± 9.23*	Up to 100pg/ml
Diabetes		

Citation: Hamouda AF. A biochemical study of chronic stress and chronic inflammation fibromyalgia. *Pharm Pharmacol Int J.* 2018;6(3):234–243. DOI: 10.15406/ppij.2018.06.00181

Table Continued

Test	Result	Normal Range
F.B.S.	80±11.04*	70–110mg/dl
P.P.B.S.	110±5.29*	Up to 140mg/dl
Stool		
Occult blood by Immunological technique	Negative	Negative
Complete stool analysis	Normal	Negative
Stool(culture) Shigella	Passed	Negative
Urine		
Complete urine analysis	Normal	Normal

Data was expressed using Mean±SD *: Statistically significant at p≤0.05

Discussion

Stress is a state of unsafe homeostasis excited by a psychological, environmental, or physiological stressor. With the rapid development of science and technology, as well as economy and strong social competition, the nature of stress has changed dramatically. Stressful events incite multiple neurochemical, neurotransmitter and hormonal alterations by mainly activating the sympathetic nervous system (SNS) and the hypothalamic-pituitaryadrenal (HPA) axis. When stress stimuli are under control, the body physiologically responds to tenseness. SNA and HPA axis are woken up to release chemical mediators to protect our body from stress.[20–24] SNS affect efferent vagus nerve interfaces with parasympathetic control of the heart, lungs, and digestive tract. For instance, catecholamines are elevated to increase heart rate and blood pressure, which help us to fight or flight. But with constant and sustained stress led to disorder in heart rhythm, this agrees with the present study where the patient diagnosed with anxiety and disorder of heart rhythm as a result of severe stress. This appropriate body reaction was called ''allostasis''. This state is advantageous to our survival and restoration, and this considers as evolutionarily adaptive benefits. However, when stress stimuli are prolonged or over excessive, in another word, chronically raised allostasis direct to pathophysiology. In the last two decades, accumulating evidence showed that severe or prolonged (chronic) stress followed in progressed risk for physical and psychiatric disorders, which is called stress-related disease. Stress is the current risk factor of 75%–90% diseases, including the conditions which cause the foremost morbidity and mortality. According to the recent review, the most common stress-related diseases are cardiovascular diseases (CVD, i.e., hypertension and atherosclerosis), metabolic diseases (i.e., diabetes and non-alcoholic fatty liver disease, NAFLD), hemolytic anemia, Fibromyalgia syndrome (FMS), psychotic and neurodegenerative disorders (i.e., depression, Alzheimer's disease, AD and Parkinson's disease, PD), cancer and other.[23–25] The inclusion criteria of the present study included agreeable BMI and healthy lifestyle eating pattern. However, the patient diagnosis with low or high blood pressure anxiety, a disorder of heart rhythm and danger stress score. In the extensive epidemiological study, scientists found that low blood pressure was associated with increased prevalence of anxiety and depression which is not caused by cardiovascular disease. This result agrees with the present study where there is low blood pressure as compared to the standard range; this may be stress that induces a change in both SNA and led to change in heart rate, blood pressure and biochemistry of life.[22–26]

Biochemistry of life includes a group of hormone and neurotransmitter that should be in homeostasis to have a happy life and help to maintain stress. The biochemistry of life and human brain includes classical monoamines, Histamine, Catecholamines, and Classical Tryptamines. Where Catecholamines contains 1) Adrenaline (Ad, Epinephrine, Epi), 2) Dopamine (DA), 3) Noradrenaline (NAd; Norepinephrine, NE). Norepinephrine considers as a neurotransmitter in the brain that knows as adrenalin; a hormone initiated during the activation of the stress response. On the other hand, 5-Hydroxytryptophan (5-HTP) is the intermediate metabolite of the essential amino acid L-tryptophan (LT) in the biosynthesis of sleep hormone serotonin, and it is important in FM modulation. A lot of studies indicated that therapeutic administration of 5-HTP had been shown to be effective in healing a broad class of situations, including stress, depression, fibromyalgia, binge eating associated with obesity, chronic headaches, and insomnia. The biochemistry of life can change by stress such as family problem, the way of teaching in childhood, discrimination to entering in school or faculty, stress due to study, interference of people in a person life, blaming from other. Unfortunately, sustain and accumulative stress can lead to an asymmetry in body hormone and neurotransmitter, for example, Norepinephrine, epinephrine, and dopamine that depended on each other as well as Serotonin. In humans, catecholamines and phenethylaminergic trace amines are obtained from the amino acid phenylalanine. It is well established that dopamine is manufactured from L-tyrosine via L-DOPA; however, recent proof has revealed that CYP2D6 is expressed in the human brain and catalyzes the biosynthesis of dopamine from L-tyrosine via p-tyramine, it considers as a minor pathway.[25,26] The stress response is self-regulating, ready to respond to a potential threat and then back down once the warning is lifted. When someone is continuously experiencing environmental stress, this is considered the danger that keeps the stress response system continually turned on. Leaving the stress response on consistently creates a dangerous and potentially life-threatening condition for the body. This process floods the body with excess hormones, raises blood pressure and elevates blood sugar levels, creating some host physical and psychological problems and led to body noise.[25–29] In other hand, dopamine functions are including reward, pleasure, involuntary movement, learning, memory, cognition, sleep, mood, prolactin

production and attention. Physical effects imbalance comprises raised heart rate, rapid breathing, hypertension, hyperthermia, anorexia, insomnia and student dilation, all tell-tale symptoms of "fight or flight" hormone stimulation. Stress also can affect serotonin that responsible for the regulatory actions of mood, aggression, appetite, and sleep, and it synthesis from tryptophan. Oxytocin is named the "love hormone" for a purpose but essentially concerns to females, although males also encode oxytocin proteins and practice them for similar uses. Norepinephrine (NE) or noradrenaline is monoamines; that displays critical physiological and psychological functions. NE is released during stressful moments to prepare us for action, like through a physical fight, after a sudden, intense noise or after being terrified. During the sensory loss, sleep or other periods of decreased sensory input, the locus coeruleus (the primary cluster of NE neurons) shows significantly diminished electrical activity, but this brain region quickly lights up with the presentation of a convincing stimulus. By dopamine stimulating the discharge of stress hormones, the response can turn from good to bad fast. If the human body fails to respond to its baseline levels at rest, the long-term consequences of activation can upset all organ processes. The "International Journal of Neuroscience" states that cortisol and other stress hormones start to chronic inflammation and will negatively influence the skin, cardiovascular, endocrine and digestive systems leaving the body susceptive to disorders such as rheumatoid arthritis and cancer. Also, it can lead to psychological problems related to anxiety, agitation, anger, attention-deficits, learning difficulties, depression, sleep disturbances and permanent memory loss.[26–29] These previous reports agree with present finding, symptoms, and patients complain in the current study as a result of stress and consequently change in body biochemistry.

In the current study, patients did the Standard Health Panel and scanned to trying to find the reasons for their complaints. The doctors recommended routine labs and x-rays done which showed normal and no fractures or any abnormality. The lab values (CBC, CMP, erythrocyte sedimentation rate) were all normal. Furthermore, lipids, liver, kidney, heart, diabetic, hormone, viruses and bacterial infection profile in the present study showed normal as compared to the reference range. Measure bone density using the X-ray absorption measurement is typical. MRI for bone and joint, also MRI brain and pituitary gland is a normal result. Also, Calcium(total) and Vitamin D showed normal value as compared to the reference range. The previous result excluded a group of Food allergy, heart, and liver, as well as stomach and bone diseases such as rheumatoid, autoimmune disorders [systemic lupus erythematosus (SLE)], osteoporosis, and Mediterranean fever (MEFV), and ASO effects, gout, H-pylori and obesity-related diseases. Only some inflammatory parameter and autoimmune analysis lab are abnormal. Also, anxiety and disorder of heart rhythm detected. In the present study, there is an elevation in amyloids A, c-reactive protein and fecal calprotectin in the patient group compared to the reference range as well as negative result in both PCR for Familial Mediterranean Fever Gene Mutation and Rheumatoid factor. The change in inflammation marker may be due to chronic stress. Fibromyalgia syndrome (FMS) is a prevalent chronic extensive pain syndrome primarily affecting women. Genetic risk factors are known to contribute to the etiology of the syndrome. Clinical features show that FMS and familial Mediterranean fever (FMF) have some overlapping symptoms.[30] Mediterranean fever (MEFV) gene has previously been identified as being responsible for FMF but in our study the result of PCR for Familial Mediterranean Fever Gene Mutation (FMF) is negative, and the result is confirmed two times. Also, rheumatoid arthritis absent finding confirmed tow time.

In the present study, there is an elevation in both amyloids A, c-reactive protein and fecal calprotectin in the patient group compared to the reference range. Amyloidogenesis seems to develop in only a minority of patients with active, long-standing inflammatory diseases, which show that significant disease-modifying factors may help modulate the occurrence of AA amyloidosis, the rate of AA amyloid fibril deposition in tissues, or induction of tissue damage in this form of amyloidosis. The persistent inflammation caused for example by RA is associated with increased release of the proinflammatory cytokines interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF) α. These cytokines induce markedly increased synthesis of the acute-phase protein SAA by hepatocytes. Amyloids are insoluble fibrous protein aggregates according to specific structural traits. Abnormal increase of amyloid in organs may lead to amyloidosis and may play a role in various diseases. The name amyloid comes from the first wrong classification of the substance as starch (amylum in Latin), based on crude iodine-staining techniques. For a period, it was discussed whether or not amyloid deposits were fatty or carbohydrate deposits until it was finally determined that they were, in fact, deposits of proteinaceous mass. The underlying molecular abnormalities may be either acquired or hereditary, and more than 20 various proteins can form clinically or pathologically essential amyloid fibrils in vivo. Amyloidosis is a dysfunction of protein conformation and metabolism that results in the deposition of insoluble amyloid fibrils in tissues, which causes organ dysfunction; systemic amyloidosis is described by the failure of various organs and the presence of amyloid precursor protein in the serum. Reactive amyloid A (AA) amyloidosis is one of the most severe difficulties of several chronic disorders and chronic inflammatory disorders, persistent inflammation, particularly rheumatoid arthritis (RA), and indeed, most patients with reactive AA amyloidosis have an underlying rheumatic disease. An extra-articular complication of RA, AA amyloidosis is a severe, potentially life-threatening disorder caused by deposition in organs of AA amyloid fibrils, which derive from the circulatory acute-phase reactant, serum amyloid A protein (SAA). AA amyloidosis secondary to RA and chronic inflammation is thus one of the intractable maladies seen in patients with collagen vascular diseases and is an exceptional yet essential complication of RA.[30,31]

In the present study, we announced that the elevation of Amyloid a protein and c-receive protein result from fibromyalgia that results from persistent chronic inflammation due to sustained stress. Large frames of evidence indicate that stress can initiate the inflammatory response in the brain as well as peripheral tissue, by exists communication between the neuroendocrine and immune systems. Stress stimulates the HPA axis through the hypothalamic secretion of corticotropin-releasing hormone (CRH), which usually overcomes immune responses through the discharge of glucocorticoids (GCs) from the adrenals. GCs are one of the principal stress hormones released during stress response that are well recognized for their immunosuppressive and anti-inflammatory characteristics.[20–23] Studies during the 1970s and 1980s exhibited that GCs restrained lymphocyte proliferation and cytotoxicity. Further, GCs reduce the expression of several pro-inflammatory cytokines (e.g., tumor necrosis factor a (TNF-a), interleukin-6 (IL-6)) and improve the appearance of anti-inflammatory cytokines (e.g., IL-10, TNF-b). Stress can induce low or high cortisol level. Where stress influence neurons in hypothalamus through corticotropin-releasing

hormone (CRH) inducer to cortisol modulation change balance and led to cortisol deregulation consequences alter the balance between anti-inflammatory and pro-inflammatory cytokines,[29–31] as agree with the present study. The increased in a release of the proinflammatory cytokines interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF) α induce markedly progressed synthesis of the acute-phase protein serum amyloid A protein (SAA) by hepatocytes, the concentration of that can be 100 to 1000-fold more significant than normal in Rheumatoid Arthritis. Furthermore, as a result of increases, interleukin-6 led to increasing C-reactive protein (CRP).[31,36] According to the present study, fibromyalgia FM is life-threatening secondary amyloidosis is the primary long-term complications of the disease where amyloid A and c reactive protein are secondary to sustain inflammation due to constant and accumulated stress and led to constant pain. The present explanation is chronic accumulation stress called to FM and autoimmune disease.

The present study showed an elevation in Faecal calprotectin; Faecal calprotectin is a biochemical determination of the protein calprotectin in the stool. Raised fecal calprotectin indicates the movement of neutrophils to the intestinal mucosa, which occurs through intestinal inflammation, including inflammation induced by inflammatory bowel disease. As we mentioned before, stress led to FM and IBD through many mechanisms of action. As, stress affects both the hypothalamic–pituitary–adrenal axis, and sympathetic nervous system (SNS). Activation of these pathways leads to the production of glucocorticoids, epinephrine, norepinephrine (NE), and acetylcholine (ACh), which interact with receptors on cytokine producing cells that ended with activation of inflammatory triggers as we discussed before.[20,25, 26,29,30] Epinephrine and norepinephrine activate intracellular transcription factors (e.g., nuclear factor-κB and activator protein 1) that bind to cis-regulatory DNA sequences to up-regulate inflammatory gene expression. When this occurs, and immune response genes are expressed, DNA is transcribed into RNA and then translated into protein. The resulting change in cell function leads to the production of proinflammatory cytokines (e.g., interleukin-1β [IL-1β], interleukin-6 [IL-6], tumor necrosis factor-α [TNF-α]) that signal the brain to induce cognitive, emotional, and behavioral alterations. That include several hallmark symptoms of depression (e.g., sad mood, anhedonia, fatigue, psychomotor retardation, altered appetite and sleep, and social-behavioral withdrawal). The present study showed elevation in Calprotectin, this due to chronic and sustain stress led to chronic inflammation that increases AA amyloidosis, decreased GI motility causes bacterial overgrowth, bile acid deconjugation, and consequently diarrhea, steatorrhea, and severe malabsorption. Pathogenic events involved in amyloid A (AA) amyloidogenesis together with the stress that induces IBD led to elevated calprotectin. The second reason to elevated Calprotectin is the imbalance of SNS that control efferent vagus nerve interfaces with parasympathetic and control of the heart, lungs, and digestive tract and result in imbalance modulation of these organs and led to the problem such as inflammatory bowel disease, IBD.[20–25] The previous finding agrees with the present study, where the patient cry from a problem in the heart and breath rate and IBD. And by exciting primary afferent nerve fibers in the vagus nerve, which relays information to brain systems that regulate mood, motor activity, motivation, sensitivity to social threat, and arousal. Although these neurocognitive and behavioral responses are adaptive during times of actual danger, these social signal transduction pathways can also be started by purely symbolic, anticipated, or imagined threats-that is, situations that have not yet occurred or that may never genuinely occur. Moreover, activation of these pathways can become self-promoting over time due to neuro-inflammatory sensitization and, as a result, remain engaged long after an actual threat has passed. In such instances, these dynamics can increase the risk for depression in the short-term and possibly promote physical disease, accelerate biological aging, and hasten mortality over the long run, if it is continuous or accumulated stress it will lead to conditions such as diabetes, fibromyalgia or IBD or other and constant pain.[21–36]

The stories start from early childhood. Chronic stress begins to children at home, school, and all surrounded environment. For example, in school and university, they continue to tell us that the exam is the only way that determines our skills. They stress badly effect on us but not pushing us to our future wisely. In the present study, the participate female Egyptian have chronic stress that leads to chronic inflammation. There are many types of stress that Egyptian female faces from the time of born until the time of death include Racism, heavy responsibility, persecution of all kinds, and denial of the favorite. Egyptian woman all the time have no choice, she pushed to everything in her life under the persuasion and intervened of others in her life beneath her sense of fear. For instance, Egyptian women's rate of assistance in the labor force has risen dramatically in the past two decades. Driven by economic stress, the majority of Egyptian women, who are also wives and mothers, entered the labor force and are combined into the market economy through employment in governmental agencies, and other in low-paying clerical jobs.[37–39] Although the economic pressure on the family influences Egyptian women to seek employment, cultural values continue to support the traditional roles of Egyptian women and, therefore, paid work for women leads to conflicting emotions and fear of default of women's primary tasks. So, they all the time under stress, anxiety and hard work to prove and do all type of responsibility.[37–39] When women are predominantly responsible for family responsibilities, the stress, in dealing with struggling for demands while trying to cope with inequities. It is likely to have adverse consequences on their lives and, consequently, on their health[37–39] and on her children and family too, so stress is in the closed cycle from children and adult. Women in all positions have more than their health potential. The women in all scientific or social positions are exposed to racism in all its forms. All this behavior and factors considered as building the initiated the chronic stress and primary unite of inflammation in the body. At the point when the stress increase and accumulate, it makes noise inside the human cells that led to the severe problems that can make a person suffer during his life and even led to death. The person starts seeking all specialist without no benefits. All of the specialists said you are nervous; an anxious person has no physical problem, keep calm. But how to reverse that chronic stress and inflammation? For example, stress due to Family and school stress, discrimination in handling, command of opinions can ameliorate. But there is more severe stress like war, famine, POW, seek refuge more difficult, so we should try to make life easy and look to the measurable part of our lives to improve stress. Still, you do have fun, change fun with work and change work with joy, make it cycle between work fun and vacations and did what you love; in this is the actual fun. Even people who have a fun life they need to change, to avoid dopamine resistance. By this way you do not rely on one method or approach, to sense dopamine without resistance and float dopamine in the brain that led to difficult to reach the satiety. So alternate mood between fun and work that can help in the maintenance of dopamine in the brain and decrease stress and body inflammation.

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In eventually, chronic stress has been connected with both HPA and SNS axis hyperactivity and hypoactivity like a noise inside the human body. As a result, stressful events influence multiple neurochemical, neurotransmitter and hormonal alterations by mainly activating the sympathetic nervous system (SNS) and the hypothalamic-pituitary-adrenal (HPA) axis. Furthermore, stress induces neurons in hypothalamus through corticotropin-releasing hormone (CRH) inducer to cortisol modulation change and led to cortisol deregulation consequences alter the balance between anti-inflammatory and pro-inflammatory cytokines. The conclusion is both the imbalance and increased in a release of the proinflammatory cytokines interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF) α induce markedly progressed synthesis of the acute-phase protein serum amyloid A protein (SAA) by hepatocytes and c- receive protein and led to autoimmune disorder and IBD. The present explanation is chronic accumulation stress led to FM and autoimmune disease sustained pain and other previous symptoms that patients complain from it as we mentioned before. Do something you love do not stack in routine, change to enhancement your dopamine and have the satisfaction of your life, may decrease your body inflammation

Conclusion

There is a significant relationship between chronic external stress, fibromyalgia, inflammatory parameters and constant chronic pain in 50 females Egyptian population.

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Conflict of interest

Author declares that there is no conflict of interest.

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