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Review Article

Impact of Chronic Stress on Cardiovascular System: Libyan Conflict Health Perspective Part 2: Mechanisms and Treatment Strategies

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Abstract

Recent studies have provided clear and convincing evidence that chronic stress contributes significantly to the pathogenesis and expression of cardiovascular diseases (CVDs). This bibliography is a systematic review on the impact of chronic stress on the cardiovascular system with a special reflection on the Libyan conflict. It is divided into two parts, Part 1 deals with types of chronic stresses, while Part 2 deals with mechanisms involved in chronic stress and their treatments. Medline/PubMed, Google Scholar, and Scopus databases were used to search for peer-reviewed papers dealing with the review theme. Mechanisms responsible for the development of chronic stress are either behavioral or biological. Behavioral factors include lifestyles (e.g., smoking, alcohol, and physical inactivity). Biological mechanisms include sympathetic overdrive, hypothalamic–pituitary–adrenal axis overactivity, and low activity of central gamma-aminobutyric acid. Chronic stress managements and treatment strategies include psychological treatment like cognitive behavioral interventions, breathing techniques like Yoga and/or pharmacological treatments like selective serotonin reuptake inhibitors, and drugs that inhibit sympathetic hyperactivity.

Keywords: Chronic stresses, mechanisms of chronic stresses, treatments of chronic stresses

Introduction

It is generally agreed that stress, at various levels, has serious psychological and physical effects that appear in the form of physical, psychological disorders, and chronic diseases.[1,2] A wide variety of psychological and psychosocial stresses have been associated with cardiovascular diseases (CVDs). Once diagnosed with psychological disorders, people with CVDs must be treated safely and effectively.

The intermediate processes through which psychological stress increases the risk of CVDs are incompletely understood. An understanding of these processes is important for treating psychological stress in order to reduce CVDs risk and consequences. Several pathophysiological mechanisms have been proposed to explain these relationships, including sympathetic nervous system activation, hypothalamic–pituitary–adrenal (HPA) axis dysregulation, platelet activation, and inflammation.[3] Behavioral factors have been implicated, such as nonadherence to healthy lifestyle and physical inactivates.[4]

In light of the foregoing discourse and the fact that Libyan community has been exposed to different types of stresses, it was decided to study the associations between stress and the incident and prognosis of CVD worldwide with a special reflection on the Libyan conflict. This work is divided into two parts, Part 1 deals with types of chronic stress, while Part 2 deals with mechanisms involved in chronic stress and their treatments. Medline/PubMed, Google Scholar, and Scopus databases used to get peer-reviewed papers dealing with the review theme. The words/strings used for search and inclusion criteria included but not limited to: stress, CVDs and relationship to stress, psychological stress, types of chronic stress, mechanisms of chronic stress, treatments of chronic stress, Libya, Libyan patients, Libyan conflict.

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Thirty-seven references used in writing the second part of this paper.

Mechanisms Related to Chronic Stress

A number of biobehavioral mechanisms have been proposed to underline the relationship between stress and CVD including the followings [Table 1].

Lifestyle (Behavioural)

It was reported that stressed individuals intend to be smokers, heavy alcohol users, and physically inactive.[5] Psychological stress and behavioral (smoking, alcohol, and physical activity) measured in a prospective study of 6576 healthy men and women over an average follow-up of 7.2 years revealed an incidence of 223 CVD events (63 fatal), indicating that the risk of CVD increased in relation to presence of psychological stress combined with unhealthy lifestyle.[5] This signifies the importance of health behavior changes in order to reduce CVD risk in stressed individuals.

Physiological Factors

Chronic exposure to stress leads to hormonal and endocrine abnormalities, which may be related with some diseases like CVD. The most important physiological responses involved are the sympathetic nervous system, HPA axis, and abnormality in the inhibitory gamma-aminobutyric acid (GABA) system [Table 1]. However, it should be pointed out that some of these factors may be the results rather than the cause of chronic stress.

Sympathetic Overdrive

Chronic psychological stress leading to hyperactivity of the sympathoadrenal axis might contribute to CVD through increased catecholamines (noradrenaline and adrenaline) effects on the heart, vasculature, and platelets functions. Catecholamines acting on the alpha-2 (α_2) adrenergic receptors on platelets membrane leading to increased release of platelet products such as beta-thromboglobulin and serotonin that are responsible for platelets aggregation and endothelial dysfunctions.[6] Moreover, chronic sympathetic activation can lead to downregulation of beta-adrenergic receptors in the heart (decreasing cardiac functions) and peripheral vessels (increasing peripheral resistance and hence blood pressure), making the load over the heart worse. This will end up in CVD.[7]

In addition, chronic stress has also been linked with increased level of plasminogen activator inhibitor-1, consequently increasing the chance of fibrin deposition by decreasing spontaneous fibrinolysis and hence blood coagulation.[8]

Therefore, chronically elevated sympathetic overactivity may lead to higher incidence of CAD as a result of the load exposed over the heart, increased peripheral resistance and increased platelets aggregation.

Hypothalamic–pituitary–adrenal Axis Overactivity

Individuals who live under chronic life stress are exposed to prolonged elevated cortisol level and impairment of feedback control of the HPA axis.[9] Elevated cortisol may be a mediating factor between stress and CVD. For example, cortisol inhibits the growth hormone (GH) and gonadal axes exacerbating visceral fat accumulation. This is supported by the fact that GH deficiency is associated with higher relative risk for premature CVD.[10] Moreover, cortisol by itself is a potent stimulus to visceral fat. Excess visceral fat causes in its turn dyslipidemia along with insulin resistant hyperinsulinsim and finally atherosclerosis.[11]

Abnormality in Benzodiazepine-gamma-aminobutyric Acid System

GABA is the main inhibitory neurotransmitter in most brain areas through its $GABA_A$ type receptors that increase chloride conductance causing neuronal hyperpolarization. $GABA_A$ receptor macromolecules contain the binding site of several allosteric agonists such as benzodiazepines and barbiturates.[12] GABA plays an important role in homeostasis during stress and alterations in GABAergic systems have been implicated in several psychological disorders including anxiety disorders,

Table 1: Mechanism related to chronic stress and their consequences

Mechanism	Consequences (reference)
Lifestyle (behavioral)	Smoking, alcoholism, and physical inactivity increased risk of CVD[5]
Physiological	
Sympathetic overdrive	Increased noradrenergic activity: • On blood vessels increased peripheral resistance, which will increase BP and load on the heart[6] • α_2 effect increases platelet aggregation[6] • Downregulation of beta-receptors will decrease cardiac functions and increase peripheral resistance (β_2 are vasodilator)[7]
HBA overactivity	Increase cortisol levels and impairment of feedback mechanisms will lead to: • Decreased GH resulting in premature CVD[10] • Accumulation of visceral fat resulting in atherosclerosis[11]
Abnormality in Bz-GABA system	GABA is inhibitor of HBA axis, therefore, decrease in GABA will result in HBA overactivity[14] • Chronic stress in animals decreased GABA neurons in the orbitofrontal cortex[15] • Low plasma GABA levels in human exposed to PTSD[16] • Bz binding sites on GABA macromolecule in prefrontal cortex decreased in human exposed to PTSD[17]

CVD: Cardiovascular disease, HBA: Hypothalamic-pituitary-adrenal axis, Bz: Benzodiazepines, GABA: γ-aminobutyric acid, PTSD: Posttraumatic stress disorder, GH: Growth hormone

depression, (PTSD). In addition, it has been suggested that the HPA activity is strongly regulated by GABAergic input to parvocellular neurons in the hypothalamic paraventricular nucleus.[13] Animal studies have shown that chronic stress causes disinhibition of the HPA axis due to functional alterations in GABAergic input to the paraventricular nucleus which could contribute to the observed disinhibition of this axis.[14] Consequently, if this takes place in humans, then the overexposure of the brain to glucocorticoids may precipitate stress-related disorders like depression. Chronic stress in rats has been reported recently to specifically reduce the density of calbindin-positive GABAergic neurons in the orbitofrontal cortex.[15] The clinical significance of this effect is not known but might explain the defect in memory and goal-directed behavior that takes place in human during chronic stress.

Low GABAminergic activity was also reported in human exposed to different types of stresses. It has been suggested that low plasma GABA levels after a traumatic event may predict subsequent development of PTSD.[16] The allosteric benzodiazepines receptors binding in the prefrontal cortex were decreased after combat-related PTSD.[17] Moreover, a decreased platelet peripheral-type benzodiazepine receptors density was observed in the posttraumatic stress disorder patients compared to controls.[18] This might explain the fact that the early administration of benzodiazepines to trauma survivors with high levels of initial distress did not have a noticeable beneficial effect on the course of their illness while reducing physiologic expression of arousal.[19]

In conclusion, GABA might have a role in chronic stress through the HPA axis and that low GABAminergic activity is predictive of PTSD development and low responses to benzodiazepine treatments.

Therapy Strategies in Chronic Stress

The keys to managing chronic stress involve recognizing its presence and making a commitment to do the things needed to decrease stress levels. This is done usually through psychological managements. Pharmacological treatments should be applied to individuals who do not respond very well to psychological intervention [Table 2].

Psychological Therapy

Psychological Intervention including individual or group psychotherapy, support, and stress reduction are used as treatment for stressed CAD patient. The aim of these interventions is to reduce psychological distress, which in theory would ultimately improve clinical outcomes and increase the quality of life.[20]

Most stress management strategies require a personal commitment to taking the time to practice them on a daily basis. In ischemic heart disease life stress monitoring program, patients who were assigned to usual care or psychological intervention after a couples years of follow-up had greater reduction in distress and decreased mortality (showed reduced ischemia and were less likely to suffer a cardiac event). These benefits appeared to persist for up to 5 years among patients receiving stress management training.[21]

More recently, cognitive behavioral therapy (CBT–a psychosocial intervention) is extensively used for improving mental health. CBT focuses on the development of personal coping strategies that target solving current problems and changing unhelpful patterns in cognitions (e.g., thoughts, beliefs, attitudes, behaviors, and emotional regulation). It was originally designed to treat depression and is now used for a number of psychological distresses and mental health conditions.[22]

It should be noted that psychological therapy might be an alternative for cardiac patients who cannot tolerate medications or may prefer nonpharmacological or counseling approach to treatment. As well, many patients with moderate-to-severe psychological stress may respond better to combination of pharmacological and psychotherapy than to either treatment alone.[23]

Table 2: Treatment of chronic stress and their consequences

Treatment	Consequences (reference)
I. Psychological Therapy: requires personal commitments	
A) Psychological intervention	Two years intervention decreased mortality from CVD that persisted for 5 years.[21]
B) Cognitive behavioral therapy (CBT)	It is a coping strategies that target solving current problems and changing unhelpful patterns in cognitions improving mental health conditions.[22]
II. Pharmacological Therapy: given to patients not responding to psychological therapy	
A) SSRI (e.g. Fluoxetine)	Has a dual role, treating psychological distress and inhibit platelets activation.[28]
B) Bz (e.g. lorazepam)	No beneficial effect plus problem of tolerance and dependence.[29,30]
C) Inhibitors of sympathetic activity	
• Propranolol (β blocker)	Dissociate the state of sympathetic arousal from their recollection reducing symptoms of PTSD.[34]
• Clonidine (α2 agonist)	Inhibits sympathetic outflow centrally reducing peripheral symptoms of sympathetic overactivity.[35]
III. Other Measures	
A) Physical activity and exercise.	Promotes release of endorphins centrally decreasing distress symptoms.[36]
B) Breathing techniques (e.g. Yoga).	Decreases endocrine release, reduces anxiety and symptoms of PTSD.[37]

CVD: Cardiovascular disease. CBT: Cognitive behavioural therapy. SSRI: Selective serotonin reuptake inhibitors. Bz: Benzodiazepines. PTSD: Posttraumatic stress disorder

Pharmacological Therapy

Individuals who do not respond very well to psychological intervention and other nonpharmacological treatments will usually respond to pharmacological therapy medications. Pharmacological therapy is delivered according to certain guidelines.[24] Suggested medication includes selective serotonin uptake inhibitors, benzodiazepines, and adrenergic beta-receptors blockers.

Selective Serotonin Reuptake Inhibitors

Serotonin (5-hydroxytryptamine) has been suggested to be involved in several psychiatric disorders including depression.[25] Moreover, serotonin plays an important role in platelets aggregation.[26] Enhanced platelet activation has been suggested as a possible mechanism contributing to the increased cardiac risk associated with psychological distress.[27] Therefore, serotonin may contribute to the development of not only psychiatric morbidity but also to cardiovascular risks. Selective serotonin reuptake inhibitors (SSRIs, e.g., fluoxetine and paroxetine) will increase the availability of serotonin by inhibiting its reuptake (the physiological mechanism responsible for the inactivation of serotonin) playing a dual role peripherally and centrally. Therefore, SSRIs might represent an attractive class of dual agents for treating psychological distress as well as protecting patients from secondary vascular events by simultaneously inhibiting platelet activation.[28]

The Benzodiazepines

The benzodiazepines (e.g., diazepam, alprazolam) is the drug of choice for the treatment of generalized anxiety disorder. However, contrary to expectations, the early administration of benzodiazepines to trauma survivors with high levels of initial distress did not have a salient beneficial effect on the course of their illness, while reducing physiologic expression of arousal.[19,23] Moreover, the benzodiazepines carry the risk of producing tolerance and dependence that might complicate the psychological condition of the patient.[31]

Drugs that Inhibit Sympathetic Hyperactivity

As it was mentioned earlier that chronic stress could result in overactivity of the sympathoadrenal system, it has been hypothesized that remembering and restoring traumatic memories can stimulate sympathetic arousal with its negative consequences on CV functions.[32] It was postulated that a beta-blocker like propranolol could dissociate the state of sympathetic arousal from their recollection.[32] This was found true in a clinical study published more recently where administration of propranolol in 6 weekly sessions before reactivation of a traumatic memory was more effective than placebo in reducing symptoms of PTSD in adults.[33] An older study done on Vietnam veterans with PTSD has shown that propranolol reduced the number of nightmares, recollections of trauma, hypervigilance, insomnia, startle responses, angry outbursts, and other arousal symptoms.[34]

Clonidine is a centrally acting α_2 agonist that reduces central adrenergic activity by reducing the activity in the locus coeruleus. Similarly, clonidine had been shown to reduce nightmares, improve sleep, decrease explosiveness, and reduce hyperalertness and other symptoms of sympathetic overactivity.[35]

Other Intervention Management

Alternative treatments other than psychological or pharmacological treatments include the followings:

Physical Activity and Exercises

Aerobic exercise and cardiac rehabilitation can reduce the psychological distress symptoms in addition improve cardiovascular fitness.[36]

Breathing Techniques

It was found that for chronically impaired autonomic system associated with increased coronary risk factors, breathing techniques increases parasympathetic drive and calming the stress response system. Breathing techniques like Kriya Yoga were reported as well to decrease the endocrine release of hormones and decrease anxiety and other psychological stresses like PTSD.[37]

Conclusion

Chronic stress is a high-risk factor for CVD and poor health in general. Different mechanism and different treatment strategies have been investigated by numerous studies all over the world. It is generally agreed that the key to managing chronic stress involve recognizing its presence and making a commitment to do the things needed to decrease stress levels and avoid its devastating consequences. Libyan population has been exposed to different types of stresses, especially in the last 7 years. The magnitude of the consequences of these chronic stresses on the overall health of Libyan population is not known. The facts presented in this papers (Part 1 and Part 2) suggest that Libyan nation is on the verge of a stress-induced public health crisis. The scale of this crisis will not be known without epidemiological studies on the Libyan population, especially the youth.

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Conflicts of interest

There are no conflicts of interest.

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ملخص المقال باللغة العربية

تأثير الضغط المزمن على الجهاز القلبي الوعائي: منظور الصحة للصراع الليبي.

الجزء الثاني: آليات الضغط المزمن وسبل علاجه.

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قدمت الدراسات الحديثة أدلة واضحة ومقنعة على أن الضغط المزمن يساهم بشكل كبير في الأمراض القلبية الوعائية. هذه الدراسة هي مراجعة منهجية لتأثير الضغط المزمن على نظام القلب والأوعية الدموية مع تأمل خاص في الصراع الليبي. قسم هذا البحث إلى جزئيين، الجزء الأول يتحدث عن أنواع الضغوطات المزمنة، في حين أن الجزء الثاني يتناول الآليات التي تسبب الضغط المزمن وعلاجاتها. تم استخدام Medline/PubMed وscholar google وقواعد بيانات Scopus للبحث عن الأبحاث المناظرة التي تتناول موضوع المراجعة. الآليات المسؤولة عن حدوث الضغط المزمن هي إما سلوكية أو بيولوجية. وتشمل العوامل السلوكية أنماط الحياة (مثل التدخين والكحول والخمول البدني). وتشمل الآليات البيولوجية زيادة نشاط الجهاز العصبي الودي، زيادة نشاط محور الغدة النخامية والغدة الكظرية، النشاط المنخفض للحامض الأمينيوبيوتريك المركزي (GABA). تشمل إدارة الضغط المزمن واستراتيجيات علاجها، العلاج النفسي مثل التدخلات السلوكية المعرفية، وتقنيات التنفس مثل اليوجا و/أو العلاجات الدوائية مثل مثبطات إعادة امتصاص السيروتونين الانتقائية والأدوية التي تمنع فرط نشاط الجهاز العصبي الودي.

الكلمات المفتاحية: الضغوط المزمنة، آليات الضغوط المزمنة، علاج الضغوط المزمنة.