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Review Article

A REVIEW ON SECONDARY MANIFESTATIONS OF STRESS

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ABSTRACT

Stress is the body's general reaction to any demand placed on it. However, in today's lifestyles, people often overlook stress or fail to recognize it as a serious illness condition. People are frequently confronted with challenging situations in today's environment. Excessive stress has been linked to the development of a number of disorders. If untreated, it may eventually lead to death. Various surveys conducted reports that everyone in a developing world is stressed in some or other the way. Statistics suggest that female experience more stress than male; it might be moderate or persistent, depending on the stressor. In mild cases it can be addressed by listening to music, reading books, and so on, but it cannot be remedied in cases of chronic stress. Chronic stress has been linked to the development of a wide range of significant diseases, including behavioural disorders (depression, anxiety), hypertension, heart disease, diabetes, and gastrointestinal disorders. In this article, we have discussed about some of the most prevalent major disorders that can be brought on by stress.

Keywords: Stress, Acute stress, Chronic stress, Psychological stress, Serotonin, Cortisol, Endocannabinoid.

1. INTRODUCTION

Stress is the body's general reaction to any demand placed on it. Stress-induced alterations are usually self-limiting and adaptive until they reach a "threshold" point, where they become irreversible and pathogenic [1]. It is a type of feedback survival response that improves an individual's physical and mental health [2].

Hypertension, peptic ulcer disease, immunosuppression, reproductive dysfunction, and behavioral disorders are all linked to stress. The General Adaptation Syndrome (GAS) is a collection of bodily changes caused by stress [3].

In today's world, people are more confronted with difficult situations. Excessive stress can be linked to the etiology of a variety of diseases, including depression, high blood pressure, and immunosuppression-related disorders. Stress interrupts the normal physiological condition, resulting in a state of threatened equilibrium [4-6]. Stress has been utilized as a diagnostic tool in science. It has been used as a psychological precursor to sickness, as a result of variety of conditions, or as a catch-all for worried reactions, discomfort, and the like [7]. Many individuals characterized stress in many forms. The topic has piqued the curiosity of medical professionals, social scientists, anthropologists, psychologists, and even zoologists [8]. An increase in depressive behaviors, such as anxiety, anhedonia, and learning and memory deficits, has been linked to prolonged stress [9]. When you're under a lot of pressure, the "fight or flight" response is activated in your body.

Cortisol, widely known as the stress hormone, is released as a part of this reaction. The release of cortisol from the adrenal glands is triggered when fight or flight is aroused. Cortisol circulates throughout the body and has an impact on a variety of functions, including the immunological, digestive, and cardiovascular systems. Cortisol boosts blood sugar levels as well. The cortisol response is designed to be a quick response to acute stress. When you have chronic stress, your body may find it difficult to returning to normal, and the fight or flight reaction may persist.

High blood pressure and an elevated heart rate, both of which make the heart work harder and increase the risk of heart disease, can result from this chronic stress

response [10]. Stress encourages adaptability, while long-term stress causes physical wear and tear (allostatic load). Short-term adaptability v/s long-term harm is mirrored in neural alterations, as it is in other body systems. Immune dysfunction, atherosclerosis, obesity, bone demineralization, and nerve cell atrophy are all symptoms of allostatic stress. Many of these processes are observed in major depressive disorder, and they may also be present in other chronic anxiety disorders [11]. If you don't learn to manage your stress, it can cause health concerns. When you have chronic stress, your body remains alert even when there is no threat. This increases your risk of developing health issues over time [12].

While the stress response is necessary for survival, long-term stress exposure can be harmful. Regular exposure to unpleasant stressors predicts and contributes to mental illness, such as major depressive disorders (MDD), generalized anxiety disorder (GAD), and post-traumatic stress disorder (PTSD) [13].

2. TYPES OF STRESS

The first significant distinction is the classification of acute and chronic stress. Acute stress is an unpleasant experience that lasts for a brief period of time. Chronic stress measurement is more debatable than acute stress measurement.

Table 1: Acute stress Vs Chronic stress [14]

Acute stress	Chronic stress
• Short term	• Long-term
• Stress from specific event or situation	• Repeated exposure to stress
• Quick recovery	• Not completely recovered
• Treatable and manageable.	• Complicated and require behavioral health treatment.

2.1. Acute stress

This is only a short-term stressor. You can sense it, when you slammed the brake, argue with your partner, or a steep hill is skied down. It helps you dealing with potentially dangerous situations. When you do something new or exciting, it can also happen. At one point or another, everyone experiences intense stress.

2.2. Chronic stress

This is a form of stress that lasts longer period of time like weeks or months. If you are having financial problems, an unsatisfied marriage, or work-related issues, it's possible that you have a long-term stress problem. Chronic stress might become so accustomed to, that you are unaware that it is an issue [12]. It is linked to immune system suppression, including slowed wound healing and reduced immunological responses to infectious illness [15].

Chronic stressors can take variety of forms, ranging from tumultuous marriages to stressful job environments [16]. It has been linked to psychiatric diseases. The most frequent psychiatric diseases are depression and pathological anxiety, which affect up to 25% of the global population.

It is important to maintain elevated corticosteroid hormone secretion despite negative feedback control in the context of chronic stress, as well as mount an extra corticosteroid reaction to persistent stress that has been imposed [17]. The corticosteroid receptors are divided into two categories- Mineralocorticoid receptors (MRs) and Glucocorticoid receptors (GRs) [18]. A decrease in both GR and MR levels in response to prolonged stress [19].

3. SECONDARY MANIFESTATIONS

3.1. Depression

Depression is the emotional expression of a sense of ego-impotence and helplessness in the face of narcissistic cravings that endure. Elation is the result of achieving one's narcissistic goals, whether physically or intellectually. Depression is predisposed by an infant's obsession on feelings of helplessness [20] and the major depression is a common mental illness that affects psychosocial functioning and reduces the quality of life [21]. Depression is linked to considerable functional impairment, resulting in significant social and financial costs. Stress, especially chronic stress, is linked to the development of depression, according to a large body of data. As a result, chronic stress not only works as a risk factor for depression in people, but also as a precipitating element. However, it is also possible to elicit behavioral alterations that are same as clinical depression, and a wide range of long-term stressful events that can trigger human depression and can also cause depression in animals [22-26]. The chronic stress on the other hand, is unknown to cause or cause depression.

Depression is not only a terrible condition that most

people experience during their adolescent years, but it is also a recurring one [27]. It is commonly recognized that more women than males are affected by it [28]. A poor mood or a clinical illness can be signs of depression. In both circumstances, depression and anhedonia are common, and eating, sleeping, and cognition problems are common [16]. Chronic stress contributes to the production of oxidative stress in brain regions involved in depression development [29]. Disruption in the brain are assumed to be the origin of (particular kind of) sadness or specific features of the depressive state. This question was addressed in the positive, focusing on 5-hydroxytryptamine (5-HT) and stress hormones:

- Sustained stress causes systemic alterations in the 5-HT and stress hormones that resemble the abnormalities seen in depression to a large extent.
- Significant evidence suggests that stress hormone and 5-HT disruptions in depression are pathogenic rather than only an outcome of or a result of the stress of the depressive state.

During stress begin with, stressors, or stressful experiences, frequently precede depression. Second, pre-depression stressors are substantially more common in people with depression than they are in the general population [30].

3.2. Anxiety

Anxiety is a type of tension brought on by anticipating a future occurrence- one that might or might not occur [31].The American Psychological Association defines anxiety as “emotion” that is caused by fear or something [32]. Anxiety disorders are the most frequent mental illness and psychiatric disorder in children and adolescents, accounting for 25% of all DSM-IV diagnoses at one year [33]. In case of anxiety it can be defined in a variety of ways. According to Aubrey Lewis (1970) "*Anxiety is a psychological condition marked by a subjectively felt sense of fear or a closely related emotion*". He notices that the feeling is intense, unpleasant, negative and proportional to the threat, as well as causing subjective and visible physiological problems. Anxiety has been labelled as a stimulus, a reaction, a drive, a motivator, and a personality feature at various periods [34]. Anxiety, according to Lazarus, is a stress emotion, as opposed to positive tone emotions like love, pleasure, and excitement. Stress emotions, according to Lazaru, are made up of three basic elements: affect, a need to act, and physiological changes. Endler has introduced a fourth factor, claiming that stress emotions like anxiety have an impact on cognitions as well [35].

In recent years, the majority of stress and performance researchers have adopted a multidimensional approach to anxiety, recognizing at least two distinct components. In this conceptualization, performers' anxieties about performing well and the repercussions of failing to do so are operationalized as cognitive anxiety (or worry), but performers' impressions of their physiological response to psychological stress are operationalized as somatic anxiety [36].

Anxiety disorders are associated with abnormalities in fear neurocircuitry, in which the amygdala's 'bottom-up' threat-response systems are intensified and the regulation of these processes by the prefrontal cortex (PFC) and hippocampus is disrupted. Chronic stress affects fear neurocircuitry in a similar way, boosting amygdalar activity while inducing structural degeneration in the PFC and hippocampus, decreasing PFC/hippocampus modulation of the stress response [37].

Disorders of the mind and anxiety are one among the most prevalent illness in current scenario. The majority of research has focused on how anxiety disrupts the amygdala's afferent control; only a few people have examined the anomalies throughout the body inside the neurons in the amygdala that could explain the structure's hyper excitability. As a result, finding potential substrates dysregulated in pathological situations requires elucidating signaling processes in the amygdala that regulate anxious behavior [38].

The endocannabinoid (eCB) system has lately emerged as a major regulator in stress and anxiety. Preclinical research has discovered that modulating eCB signaling modifies anxiety in humans, and similarly, cannabis use can have substantial impacts on anxiety [39].

The neurobehavioral effects of genetic or pharmacological disruption of eCB signaling include increased activation of the hypothalamic-pituitary-adrenal (HPA) axis, elevated levels of anxiety, altered stress-coping behaviors, and deficits in fear extinction [38]. The amygdala, especially the basolateral amygdala (BLA), is extremely sensitive to early-life stress (ELS), which may contribute to stress reactivity and anxiety disorders [40].Recent research has uncovered potential neuronal underpinnings of anxiety-like behavior caused by stress-induced amygdalar plasticity. Chronic immobilisation stress (CIS) but not chronic unpredictable stress (CUS), has been demonstrated to

promote dendritic remodeling in the basolateral amygdala (BLA) [41].

One of the key reasons underpinning the increased tendency for anxiety-like behaviors and pathological states is thought to be hyper activation of the amygdala in response to chronic stress; however, the methods by which chronic stress regulates amygdalar function are not fully understood. Chronic stress can impair amygdalar function, according to preclinical investigations [42].

The hippocampus and amygdala are critical parts of the brain circuitry that controls stress responses. While changes in the amygdala are more likely to contribute to the affective components of stress disorders, structural plasticity in the hippocampus may modulate cognitive aspects of behavioral deficits produced by extreme stress. Recent studies have discovered cellular and molecular correlates of stress-induced amygdaloid plasticity, which could help explain anxiety [43].

3.3. Hypertension

Hypertension is a prevalent, chronic, age-related illness that can have serious cardiovascular and renal implications. Blood pressure is regularly checked in conjunction with other risk factors for heart disease [44]. It's fair to term it a mental illness. If a person is dealing with a lot of conflict, irritation, uncertainty, impatience, or deprivation, this is a sign that they are stressed [45].

There has been a lot of research done on the link between stress and hypertension. In the short term, stress has been shown to raise blood pressure through increasing cardiac output and heart rate without affecting total peripheral resistance. Catecholamines, cortisol, vasopressin, endorphins, and aldosterone levels have been demonstrated to rise in response to acute stress, which may assist to explain why blood pressure rises [46].

Stress can increase blood pressure by causing it to rise repeatedly and by driving the nervous system to produce large amounts of blood pressure-raising vasoconstrictor chemicals. White coat hypertension, job stress, race, social context, and mental distress are all stressors that affect blood pressure. When one risk factor is paired with other stressors, the effect on blood pressure is magnified.

In general, research shows that stress isn't the direct cause of hypertension, although it's possible to influence the development. Non-pharmacologic stress management strategies such as meditation, acupressure, biofeedback, and music therapy have been shown to be effective in decreasing blood pressure and preventing the onset of hypertension.

National Health and Nutrition Examination Survey indicates that, 50 million adults in the United States have hypertension (defined to be a systolic blood pressure of greater than 139 mm Hg or a diastolic blood pressure of greater than 89 mm Hg). The cause of hypertension is unknown in 95% of these instances; hence it is classified as "essential" hypertension. Although there is no single cause for essential hypertension, the common agreement is that a number of variables contribute to blood pressure increase. Stress has become a common aspect of people's life in nowadays of 70hour weekly work schedules, pagers, fax machines, also never-ending meetings. As a result, the impact of stress affects the blood pressure is becoming more important and relevant. Despite the fact that stress does not appear to be a cause of high blood pressure directly, it can cause high blood pressure on a regular basis, this might lead to hypertension [47].

According to several studies, continuous stress may predispose individuals and animals to long-term hypertension, and particular groups are at risk of developing stress-induced hypertension. Long-term stress-induced hypertension is most likely caused by neurohormonal trophic factors that lead to arterial hypertrophy or atherosclerosis. Because the phenomena of 'white-coat hypertension' might alter blood pressure measurement, ambulatory blood pressure monitoring is becoming more common in the evaluation of hypertensive patients. Finally, relaxation techniques are increasingly being employed to treat hypertension patients [46].

3.4. Heart diseases

Heart diseases are currently the most common reason for death worldwide, accounting for one-third of all deaths. Heart disease is no longer viewed as a problem primarily affecting overworked and overweight middle-aged men in affluent countries [48]. Coronary artery disease (CAD) or coronary heart disease (CHD) is commonly detected within the first year of life, or shortly after delivery. Many cardiac abnormalities have been surgically corrected throughout childhood in recent decades [49].

The hypothalamus and brain stem activate the stress response, which aids the body's recovery from short-term physical stressors. These systems are overactive for an extended period of time, on the other hand, can

produce wear and tear and play a part in coronary artery disease [50].

In sensitive people, intense emotional stress can set off an episode of CHD [51]. Chronic stress increases the risk of coronary artery disease (CAD) and has a poor prognosis in the cardiovascular system. Although acute catastrophic events may produce acute myocardial infarction or sudden death, the National Heart Foundation of Australia found in 1988 that there was inadequate information from prospective trials that any type of "stress" reliably predicted the eventual progression of CAD [52].

Acute life event "stressors" can cause CHD, albeit determining the magnitude of the effects is difficult. Acute “stressors” might encompass everyday like bereavement as well as catastrophic events like earthquakes or terrorist attacks. Although the deleterious physiological effects of acute “stressors” as CHD triggers have been widely documented, less is known about the role of chronic “stressors” in CHD incidence and prognosis.

Workplace "stressors" are distinct from the "stressors" associated with life events discussed above. The research included in one review under psychological work characteristics was diversified, examining a wide range of concerns on an individual basis [53]. The workplace stress has been linked to an elevated risk of coronary heart disease (CHD), but the reasons behind this link are unknown [54]. Workplace stress may affect CHD directly by activating Stress-induced neuroendocrine reactions, or indirectly through unhealthy habits that increase CHD risk, such as smoking, inactivity, or too much alcohol consumption.

Autonomic nerve system is one of the major axis of neuroendocrine stress reactions (ANS). Reduced heart rate variability is a sign of repeated activation of the ANS, it was linked to work related stress among males in cross-sectional research [55-56]. Workplace stress has been associated to cortisol circadian rhythm disturbances and the development of the metabolic syndrome, which has been linked to may also effects which have been linked dysfunction of the hypothalamic-pituitary-adrenal axis [57].

Despite evidence that chronic stress is connected to an increased risk of cardiovascular mortality and morbidity, few longitudinal studies investigating the influence of cumulative occupational stress on other intermediate mechanisms have been conducted. Workplace stress, especially among younger workers, is linked to coronary heart disease and neuroendocrine stress responses. A higher cortisol awakening reaction was not linked to cumulative work stress. Work stress, on the other hand, was linked to a higher cortisol awakening response in a cross-sectional analysis. The identification of the expected neuroendocrine effect may be hampered by a 12-year lag between exposure (job stress) and disruptions in cortisol's circadian cycle [58]. If there is a reduction in the workplace stress, it also lowers the risk of coronary artery disease [50].

Chronic stress, according to research, raises the risk of coronary heart disease. In a 9-year study of 12,000 healthy guys, those who had chronic problems at work or at home were 30 percent more likely to die of CHD [59].Despite the fact that these studies give convincing evidence of mind-body links in CHD, they are not conclusive [16].

3.5. Diabetes mellitus

Diabetes mellitus is a group of metabolic disorders characterised by high blood sugar levels caused by insulin synthesis, insulin action, or both. Multiple organs, including the eyes, kidneys, nerves, heart, and blood vessels, are damaged, dysfunctional, and fail as a result of diabetes [60]. It has a variety of causes and is divided into two categories: type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) [61].

Chronic hyperglycemia in diabetes can be exacerbated by stress. Stress has been shown to have a significant impact on metabolic activity for quite some time and the energy is mobilised as a result of the fight or flight response. A variety of hormones are released as a result of stress, which can contribute to a rise in blood glucose levels. Stress has been found in human research to cause hyperglycemia, hypoglycemia, or have no effect on glycaemic status in people with diabetes [62]. In the pathophysiology of diabetes mellitus, oxidative stress plays a crucial role (DM). In addition to underlying diabetes problems, oxidative stress appears to be a pathogenic component.

All of these mechanisms, however, have one thing in common: the production of reactive oxygen species (ROS), which produces persistent oxidative stress, which leads to faulty insulin gene expression and secretion, as well as increased apoptosis.

The presence of oxidative stress is a significant component in the progression of diabetes, as it causes cellular damage that can contribute to the development of a variety of diabetic problems. The presence of cellular oxidative stress is associated with both diabetic cell damage and the development of insulin resistance.

Acute glucose variations may contribute to the development of oxidative damage. Increased generation of reactive oxygen species (ROS) can also be caused by elevated cellular glucose levels. Furthermore, oxidative stress may contribute to the establishment of diabetes by lowering insulin sensitivity and damaging the pancreas' insulin-producing cells [61].

Over the next 25 years, DM is anticipated to affect at least 366 million people globally. It is commonly acknowledged that oxidative stress caused by hyperglycaemia contributes to diabetes-related cell and tissue damage [63].

3.6. Gastrointestinal disorders

The term "stress" is used to describe a situation in which there is immediate danger to an organism's homeostasis caused by genuine ('interoceptive'; e.g., haemorrhage, gut infection) or events that are perceived (exteroceptive), to safeguard the internal environment's stability, it activates adaptive physiologic and behavioural responses [64]. It may affect the function of the gastrointestinal system in both the short and long term [65]. Physical and psychological stress are generally recognised as causes and/or modifiers of the clinical course of a variety of gastrointestinal illnesses, including peptic ulcer disease, irritable bowel syndrome, and inflammatory bowel disease [66] and the exogenous pathogenic bacteria, as well as dietary changes, can cause oxidative stress in the GI tract [67].

In general, the natural antioxidant defence system or antioxidants added to the diet counteract the generation of reactive species. When this balance is disrupted, oxidative stress develops. Numerous and diverse illnesses, including those of the gastrointestinal system, are exacerbated by oxidative stress. The Obesity-related oxidative stress appears to impact gastrointestinal motility [68].

The central stress response is mediated in part by corticotropin releasing factor (CRF). R1 and R2 are two kinds of CRF receptors. In reaction to stress, they regulate an increase in colonic motor activity and a slowing of stomach emptying.

The permeability of the intestine to big antigenic molecules increases as a result of stress. Mast cell activation, degranulation, and the depletion of colonic mucin are all possible outcomes. In reaction to stress, a cholinergically induced reversal of water and electrolyte absorption occurs in the small bowel. Colonic inflammation is also made worse by stress [65].

The psychological strain is thought to possess a crucial part in functional gastrointestinal (GI) diseases, particularly irritable bowel syndrome (IBS), by causing symptoms to worsen. In terms of their role as stressors, psychological and exteroceptive stresses differ.

- A risk factor for later-life development of a functional GI problem (Early-life trauma, such as neglect, increases disease vulnerability because stress response is permanently enhanced).
- A long-term trigger for symptom onset or aggravation (Psychosocial stresses, such as life-threatening incidents, cause transitory alterations in stress reactivity). OR
- A factor that prolongs symptom chronicity in patients with functional gastrointestinal disorders by evoking stress responses in previously non-stressful situations. (conditioned stressors, e.g. fear responses to symptoms related to a functional disease) [64].

Stress and gastrointestinal ailments, such as functional bowel disorders, inflammatory bowel disease, peptic ulcer disease, and gastro esophageal reflux disease, all of these things are being studied in depth [65].

4. CONCLUSION

In conclusion, stress has been linked to a variety of serious illnesses as a secondary disease. One of the leading causes of secondary illnesses is chronic stress. Stress has been related to psychiatric diseases like depression and anxiety, as well as hypertension, diabetes, heart disease, and digestive difficulties. Although, Stress does not directly cause multiple diseases, but it does influence their progression.

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Conflict of interest

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