

Pathophysiology of Stress: A Review

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ABSTRACT

Our over-industrialized and highly competitive metropolitan culture has added up to our stresses at many levels. The media, also in a way, provides certain “constructs” which in their turns create stress and anxiety about our bodies, levels of successes, status, gender roles and other perspectives. Sometimes violence (gendered or otherwise) along with repression, neurosis, loneliness and other psychological factors lessen the wellbeing of an individual, both physically and psychologically. Stress is body’s way of responding to the demand which is caused by both good and bad events/experiences. The body reacts by releasing chemicals in the blood to combat this demand by a complex repertoire of behavioral and physiologic adaptive responses. Stress experiences often lead to various chronic health conditions such as hypertension, coronary heart disease. To make this world a better place to live in we need to make individuals conscious of the fact that the positive health of a person depends on both the body and the mind.

Keywords: Stress, Pathophysiology, disease.

INTRODUCTION

Life exists through the maintenance of a complex dynamic equilibrium, termed as homeostasis. Homeostasis of our body is constantly challenged by internal or external adverse forces, stressors. ^[1] Stress is defined as a state of threatened homeostasis and is counteracted by a complex repertoire of physiologic and behavioral responses that reestablish homeostasis. Allostatic load develops due to persistence of chronic stressors. ^[2]

Perception of stress is influenced by one's experiences, genetics, and behavior. When the brain perceives stress, physiologic and behavioral responses are initiated leading to allostasis and adaptation. Over time, Allostatic load can accumulate, and the overexposure to neural, endocrine and immune stress mediators may have adverse effects on various organ systems, leading to

disease. ^[2] Allostatic Overload caused by chronic stress may lead to²: Decreased immune functions, Hypertension, Atherosclerosis, Increase platelet reactivity, Abdominal obesity, Diabetes mellitus, Bone demineralization, Atrophy of neurons in hippocampus and prefrontal cortex, Increased activity of amygdala, Problems in digestion, Addiction, Depression, Anxiety, Infertility. Optimal interaction of the Nervous system, Endocrine system, Immune system systems help in maintaining Homeostasis. ^[2]

The human brain can be subdivided into 3 levels: ^[1-3]

1. Vegetative level

Reticular activating system or RAS and brain stem.

RAS is the connection between brain & spinal cord.

Brain stem consists of pons, medulla and mesencephalon.

Brain stem is involved in regulation of involuntary functions of human body

2. The limbic system

Hypothalamus along with the Limbic system is involved in emotional expression and the emotion genesis. [1-3]

It has limited number of connections with Neo-cortex. Neocortical activity modifies emotional behavior and vice versa.

Limbic circuits show prolonged after-discharge following stimulation. For this unique feature, emotional responses are generally prolonged and remain sustained even after the stimuli fade off. [1-3]

3. The neocortical level

Highest level and most developed area of brain, responsible for processing of sensory information and cognition. Analysis, imagination, intuition, creativity, logic, memory, organization all are the functions of neo-cortex.

This region can override the functions of lower levels of brain and thus conscious thought can influence emotional response and also the involuntary responses like heart rate, respiration and even blood flow. [1-3]

Autonomic Nervous System: The two subdivisions of ANS, Sympathetic and Parasympathetic, are functionally antagonistic in nature and most organs receive both sympathetic and parasympathetic innervations. Emergencies that cause stress and require us to "fight or flight" response are evoked by Sympathetic system, whereas Non-emergencies which allow us to "rest and digest" are evoked by Parasympathetic responses. [1-3]

The ANS has a complex central neural organization located in various regions of the brain and spinal cord. The highest seat regulating autonomic functions is in the hypothalamus - the posterior and lateral nuclei are primarily sympathetic while anterior and medial nuclei are primarily parasympathetic. The hypothalamus is not essential for most of the sympathetic and

parasympathetic effects except in conditions of stress. [1-3]

The sympathetic system has a companion gland, the adrenal medulla, which also secretes epinephrine and nor epinephrine (i.e. plasma catecholamines). [1-3]

Neuroendocrine System [4-6]

Neural axis

The entire central nervous system is directly or indirectly involved in the maintenance of the internal homeostasis and participates in the organization of the stress response. Specific areas of the brain have critical roles in these mechanisms. Modulation of the activity of the stress system at the level of both the hypothalamic-pituitary-adrenal axis and the central and peripheral components of the autonomic nervous system is essential for a successful adaptive response to stressors.

Stress response relies on Neuronal pathways of cerebral cortex, the limbic system, the hypothalamus, the thalamus, the pituitary gland and the reticular activating system (RAS).

1. The cerebral cortex deals with vigilance, cognition and focused attention.
2. The limbic system is associated with emotional components like fear, rage, anger of the stress response.
3. Thalamus acts as a relay center and helps in receiving, sorting out and distribution of sensory input.
4. Hypothalamus coordinates endocrine and autonomic responses.

Neuroendocrine axis [7-9]

The human stress response involves a complex signaling pathway among the neurons and the somatic cells. Exposure to hostile conditions initiates the secretion of several hormones, like Cortisol, Catecholamines, Prolactin, Oxytocin, and Renin. These are considered as part of the survival mechanism. The hormones released in response to stressors are often referred to as "stress hormones". The secretion is mainly regulated by neural circuits impinging on hypothalamic neurons.

The hypothalamic-pituitary-adrenal (HPA) axis plays a vital role. This is in turn mediated by the hippocampus and the autonomic nervous system (ANS). They interact with other vital centers in the central nervous system (CNS), tissues/organs in the periphery as well as the locus Coeruleus (LC). They also coordinate other catecholaminergic, norepinephrine (NE) synthesizing cell groups of the medulla and pons. Stress stimulates the release of corticotropin-releasing hormone (CRH) from the hypothalamic Paraventricular nucleus (PVN), into the hypophysial-portal circulation. CRH induces the release of adrenocorticotropin hormone (ACTH) from anterior pituitary as well as glucocorticoids from adrenal glands.

Corticotropin-Releasing-Hormone and Catecholaminergic Neurons ^[10-16]

Central stress system activation is based on reciprocal reverberating neural connections between the PVN CRH and the catecholaminergic LC/NE neurons. CRH and NE stimulates the secretion of each other through CRH receptor1 (CRHR1) and α 1noradrenergic receptors. Autoregulatory ultra short negative feedback loops exist in both the PVN CRH and the brainstem catecholaminergic neurons. Their collaterals inhibit CRH and catecholamine secretion respectively, by inhibition of the corresponding presynaptic CRH and α 2 noradrenergic receptors. CRH and catecholaminergic neurons receive stimulatory innervation from the serotonergic and cholinergic systems. They receive inhibitory input from the gamma-amino-butyric acid (GABA)/benzodiazepine (BZD), the opioid neuronal systems of the brain, and glucocorticoids (the end product of the HPA axis).

Sympathetic nervous system, Adrenal Medulla ^[10-16]

The autonomic nervous system provides a rapidly responsive mechanism to control a wide range of functions. Cardiovascular, respiratory, gastrointestinal,

renal, endocrine, and other systems are regulated by either the sympathetic nervous system or the parasympathetic system or both.

The dorsomedial amygdala complex appears to represent the highest point of origination for the “fight-or-flight” response as a functionally discrete psychophysiological axis. From dorsomedial amygdala complex, the downward flow of neural impulses passes to the lateral and posterior hypothalamic regions ¹⁶ and continue to descend through the thoracic spinal cord, converging at the celiac ganglion, and then innervating the adrenal medulla.

The hormonal output of the neuroendocrine stress-response axis is the secretion of the adrenal medullary catecholamine: norepinephrine (noradrenaline) and epinephrine (adrenaline).

Effects of adrenal medullary axis stimulation ^[10-16]

- Increase in arterial blood pressure.
- Increase in blood supply to brain (moderate).
- Increase in heart rate and cardiac output.
- Increase in stimulation of skeletal muscles.
- Increase in plasma free fatty acids, triglycerides, cholesterol.
- Increase in release of endogenous opioids.
- Decrease in blood flow to kidneys
- Decrease in blood flow to gastrointestinal system.
- Decrease in blood flow to skin.
- Increase in risk of hypertension.
- Increase in risk of thrombosis formation.
- Increase in risk of angina pectoris attacks in persons so prone.
- Increase in risk of arrhythmias.
- Increase in risk of sudden death from lethal arrhythmia, myocardial ischemia, myocardial fibrillation, myocardial infarction.

Now we will discuss about the interaction of stress with different systems of the human body.

Stress system - Interactions with other CNS components [10-16]

The stress system in addition to setting the level of arousal and influencing the vital signs, interacts primarily with the following system:

- Mesocorticolimbic dopaminergic system (“reward” system)
- Amygdala/hippocampus complex
- Arcuate nucleus proopiomelanocortin (POMC) neuronal system [12-14]

These systems after their activation by a stressor act via specific neuronal pathways and modify the activity of the stress system. They form a complex reciprocal mechanism that fine-tunes the adaptive response. Interactions exist between the stress system and centers of the CNS which are crucial for the survival of an individual, like the thermoregulatory, appetite-satiety centers.

Mesocorticolimbic Dopaminergic System:

[10-16] The mesocortical and mesolimbic components of the dopaminergic system are innervated by PVN CRH neurons and the LC/NE-sympathetic noradrenergic system. They are activated by Catecholamines, CRH and glucocorticoids during stress. The mesocortical system contains dopaminergic neurons of the ventral tegmentum that send projections to the prefrontal cortex. The activation of these neurons centrally suppress the response of the stress system and is implicated in anticipatory phenomena and cognitive functions. The mesolimbic system also consists of dopaminergic neurons of the ventral tegmentum. These neurons innervate the nucleus accumbens and are also considered to play a pivotal role in stress response.

Amygdala/Hippocampus [10-16]

The amygdala/hippocampus complex is activated during stress by ascending catecholaminergic neurons. These originate in the brain stem or from cortical association areas. The amygdala nuclei are the principal brain locus for fear-related behaviors. Their activation is important for retrieval and emotional analysis of all the relevant stored information for any given stressor. In response to emotional stressors,

the amygdala can directly stimulate both central components of the stress system. Amygdala stimulates the mesocorticolimbic dopaminergic system. CRH neurons in the amygdala respond positively to glucocorticoids and activation of these neurons lead to stimulation of the stress system and anxiety.

CRH fibers interconnect the amygdala with stria terminalis and the hypothalamus. [10-16] The hippocampus exerts an important tonic and inhibitory influence on the activity of the amygdala, and PVN CRH and LC/NE-sympathetic systems. The hippocampus by this mechanism plays an important role in shutting off the HPA stress response. [10-16]

Arcuate Nucleus: Proopiomelanocortin (POMC) Neuronal System [3]

Arcuate nucleus of Hypothalamus produces POMC which is an opioid peptide. The Arcuate nucleus innervate and is reciprocally innervated by both the LC/NE-noradrenergic and the CRH/AVP-producing neurons. During stress system activation, Hypothalamus releases POMC derived peptides like α -melanocyte stimulating hormone (α -MSH) and β -endorphin. These two peptides again reciprocally inhibit central components of stress system. These neurons also have projections in the spinal cord and hind brain and plays important role for stress-induced analgesia by inhibiting the ascending pain pathways.

Temperature Regulation by Thermoregulatory center [11-12]

Stressors activate LC/NE-noradrenergic and PVN CRH systems. This causes an increase in core temperature of the body. CRH, when stimulated by lipopolysaccharide, which is a potent exogenous pyrogen, partly mediates the pyrogenic effects of the three major inflammatory cytokines: tumor necrosis factor- α (TNF- α); interleukin 1 (IL-1); interleukin-6 (IL-6). Psychological stress induces a rise in body core temperature through activation of thermoregulatory sympathetic premotor neurons in the medullary raphe region.

Appetite Regulation by Appetite-satiety centers ^[17-21]

Stress is implicated in the regulation of appetite by influencing the central appetite-satiety centers in the hypothalamus. Stress-induced eating behavior of obese women with binge eating disorder is characterized by a stronger motivation to eat as well as by absence of satiety perception.

CRH causes anorexia whereas NPY is orexiogenic. NPY stimulates CRH secretion via Y1 receptors, probably to counter-regulate its own actions. At the same time, NPY inhibits the LC/NE-sympathetic system and activates the parasympathetic system thus leading to decrease thermogenesis and help with digestion and storage of nutrients. Leptin, the adipose tissue-derived satiety-stimulating hormone, inhibits the secretion of hypothalamic NPY, while it stimulates arcuate nucleus POMC neurons that secrete α -MSH, a potent anorexiogen and thermogenic peptide, which exerts its effects through specific melanocortin receptors type 4 (MC4). Recently a direct effect of glucocorticoids on the regulation of appetite has been recognized.

Endocrine axis ^[22-28]

Stress can lead to acute or chronic pathological conditions (such as metabolic syndrome and atherosclerosis) in individuals with a genetically or constitutionally vulnerable background by interacting with various axes (such as thyroid and growth axis) and systems (such as reproductive, gastrointestinal and immune system) Well-established endocrine axes associated with stress responses are as follows:

1. Adrenal-cortical axis
2. Somatotropic axis
3. Thyroid axis
4. Posterior pituitary axis
5. Reproductive system

Adrenal-cortical axis: ^[29-32]

This axis starts from Septal hippocampal area and descends down to median eminence of hypothalamus. The neurosecretory cells of this region of

hypothalamus induces the secretion of CRH in hypothalamic-hypophysial portal system. ACTH stimulates Zona fasciculata to secrete two important glucocorticoids into the systemic circulation i.e. Cortisol and Corticosterone. In response to stressful stimuli glucocorticoids serve the following important actions in human body:

1. Stimulation of Gluconeogenesis.
2. Decreased glucose utilization by cells.
3. Elevated blood glucose level.
4. Reduction of protein stores in essentially all body cells except those of the liver.
5. Increases Liver and Plasma proteins.
6. Increased mobilization of fatty acids from muscle and adipose tissue and thus increases free fatty acid concentration in plasma.
7. Anti-inflammatory effects observed with high levels of Cortisol.
8. Increased susceptibility in Atherosclerotic processes and Non-thrombotic myocardial necrosis.
9. Immunity suppression.
10. Increased Ketone body and urea production.
11. Suppression of Appetite.
12. Gastric irritation.

Glucocorticoids also antagonize the beneficial anabolic actions of Growth Hormone (GH), insulin and sex steroids on their target tissues. ^[29-32] Chronic activation of HPA axis increases visceral adiposity, decrease lean body mass, suppress osteoblastic activity and cause insulin resistance

Stressful situations are associated with anorexia and profound suppression of food intake. Indeed, CRH stimulates the POMC neurons of the arcuate nucleus which, via α -MSH release, elicits anti-orexiogenic signals and increase thermogenesis. The anorexiogenic effects of CRH appear to involve the lateral septum or the bed nucleus of the stria terminalis and to be mediated through CRHR2 subtype. High cortisol and neuropeptide Y levels are found to be associated with disordered eating psychopathology independent of body mass index. Insulin and leptin play important roles in the regulation of central pathways

related to food reward. Chronic hyper activation of the stress system may lead to osteoporosis and metabolic syndrome. [29-30]

Effects of the stress system on the immune or inflammatory reaction:

Activation of the HPA axis has profound primarily inhibitory effects on the inflammatory/ immune response, as all the components of the immune reaction are inhibited by cortisol.

Both the innate and adaptive immune response are modulated by glucocorticoids. At the cellular level, alterations of leukocyte traffic and function, decreases in production of cytokines and other mediators of inflammation and inhibition of their effects on target tissues appeared to be among the main anti-inflammatory effects of glucocorticoids. [31-37] Glucocorticoids also suppress TNF- α and IL-1 β production.

Apart from immune functions such as antigen presentation, leukocyte proliferation and trafficking, secretion of cytokines, the principal stress hormones glucocorticoids and Catecholamines affect the selection of the T helper (Th) 1 versus Th 2 responses. Glucocorticoids and Catecholamines directly inhibit the production of type 1 cytokines, such as IL-12, IL-2, TNF- α and INF- γ , that enhance cellular immunity and Th1 formation and conversely favor the production of type 2 cytokines, such as IL-10, IL-4, IL-13, that induce humoral immunity and T-helper 2 (Th2) activity. [31-37]

Stress and Blood Sugar level:

Stressors have a major influence upon mood, our sense of well-being, behavior, and health. Acute stress responses in young, healthy individuals may be adaptive and do not impose a health burden in short term. But, if the threat is unremitting, particularly in older or unhealthy individuals, the long-term effects of stressors can lead to damage. The relationship between psychosocial stressors and disease is affected by the nature, number, and persistence of the stressors as well as by the individual's biological

vulnerability (i.e., genetics, constitutional factors), psychosocial resources, and learned patterns of coping. Psychosocial interventions have been proven useful for treating stress-related disorders and may influence the course of chronic diseases. [38-39]

Psychological reaction to stressors leads to the activation of the hypothalamo-pituitary-adrenal (HPA) axis, leading in turn to various endocrine abnormalities: high cortisol and low sex steroid levels, and these antagonize the actions of insulin.

An increase in visceral adiposity (increased girth) may be observed in chronic stress, which plays an important role in diabetes by contributing to insulin resistance. [38-39]

Any stressful event might be judged by people in different ways, based on factors like previous experience, psychological factors, and social influences. An event that is seen by one individual as particularly threatening might be seen as totally harmless by other individuals. But, when a situation is regarded as challenging, a specific pattern of physiological responses is elicited, known as the stress response or "fight/flight" response. These patterns of responses have developed as a result of human evolution. They are aimed at priming the individual for action, so that the situation can be dealt with by either fighting or fleeing the situation. The responses initiated by the central nervous system in response to a threat affect the entire body and are associated with different bodily systems: the autonomic nervous system, the neuroendocrine system, and the immune system. [38-39]

The sympathetic system is involved with the preparation of the body for alarm reaction. The HPA axis is of considerable importance with regard to the effects of stress on the neuroendocrine system. When encountering a stressor, the hypothalamus secretes CRH, which causes release of ACTH. ACTH travels to the adrenal cortex, and leads to the secretion of glucocorticoid hormones, cortisol in particular. In normal

circumstances, cortisol is secreted according to a circadian (daily) rhythm. Cortisol levels are found to be usually highest in the early morning and lowest in the evening. Exposures to stress may stimulate the HPA axis to release additional amounts of cortisol to maintain homeostasis and reduce the effects of stress. Cortisol influences a wide range of metabolic processes, including the breakdown of carbohydrates, lipids, and proteins to provide the body with energy. It also has an effect on bone and cell growth and may also modulate the salt and water balance. Cortisol has an immunosuppressive effect and plays an important role in the regulation of immune and inflammatory processes. [38-40]

Chronic stress has been shown to have a strong link with metabolic syndrome (MetS). MetS is an aberrance of metabolic functions resulting in abnormalities that are major risk factors for the development of cardiovascular disease (CVD) and type 2 diabetes mellitus (T2 DM). Stress stimulates the release of various hormones, which can also result in elevated blood glucose levels. [38-40]

The increase in prevalence of diabetes in urban population may be associated with decreased physical activity and increased prevalence of obesity. [38-40] It is well documented in different studies that depression, anxiety, and stress symptoms are more prevalent among diabetic individuals. In a study comparing diabetic and non-diabetic subjects following results were obtained:

1. The prevalence of severe anxiety was 35.3% vs. 16.3%
2. Severe depression was 13.6% vs. 5.9%
3. Severe stress was 46.6% vs. 21.7%. [39]

Anxiety disorders usually represent an exaggerated emotional response to the fears. People with diabetes are at higher risk for these disorders because they often live with fear greater: such as fear of hypoglycemia, complications, and the effects of diabetes in daily life. [40,41] The relationship between stress and glycemic control is very complex. Stress can affect

blood glucose level in different ways. The physiological responses are as follows: increased heart rate; peripheral vasoconstriction; elevated skeletal muscle activity; increased hormone release (pituitary, corticosteroids, catecholamines); and, inhibited insulin production, all these responses contribute to increased blood glucose levels. [41]

Psychological responses can also affect self-management abilities and can negatively influence the individual's health care practices essential for successful self-management. [42] Diabetes negatively affects physical functioning (e.g. decreased energy), psychological status (e.g. depression and stress) and social relationships. These factors in turn affect the quality of life. Health-related quality of life is modified by the impairments, functional status, perceptions and social opportunities influenced by disease, injury, treatment or policy. While considering the quality of life in diabetic patients we should take into account the following factors as these may be some of the critical components of the individual perception of quality of life:

1. The personal side of diabetes
2. The perceived burden of living with the illness
3. Different clinical features of diabetic patients and type of complications. [43]

The management of diabetics requires lifestyle modification and effective self-management strategies. Strict dietary regimen, exercise, blood glucose monitoring and medication management need to be followed and these factors increase stress levels of the patients. Comprehensive education, diabetes self-management training, follow-up and ongoing social support is required for diabetic patients and their families. These factors may help in decreasing stress levels of the subject. For some people with diabetes, controlling stress with relaxation therapy seems to be helpful. Stress decreases release of insulin in people with type II diabetes. So interventions to decrease stress may be helpful for these people. Some people with

type II diabetes may also be more sensitive to some of the stress hormones. Relaxation exercises may help by blunting this sensitivity. [43-45]

Evidence suggests that stressful experiences might affect diabetes, both in terms of its onset and its exacerbation. In recent years, the complexities of the relationship between stress and diabetes have become well established. Some studies have suggested that stressful events (sometimes referred to as stressors) and the physiological and psychological or behavioral responses to these might affect the onset and the metabolic control of diabetes. [42-45]

Relation of diabetes and psychiatry has fascinated endocrinologists as well as mental health professionals for a long time. Diabetes and psychiatric disorders share a bidirectional association. Both influencing each other in multiple ways. In spite of multifaceted interaction between the two, the issue still remains largely unstudied in India. [46]

Comorbidity of diabetes and psychiatric disorders may present in different forms:

1. The two may present as independent conditions with no apparent direct connection.
2. The course of diabetes may be complicated by emergence of psychiatric disorders.

Mood disorders include depressive disorders, and bipolar affective disorders (BPAD). Co-occurrence of diabetes and depression has long been established in clinical as well as general population studies. This co-occurrence is associated with increased chances of impairment of life as well as the risk of mortality. Risk of developing depression is 50-100% higher among patients with diabetes as compared to the general population. [47]

Stress and Lipid profile:

Cardiovascular diseases (CVD) have long been recognized as important threats to human health. Dyslipidemia plays a major role in the modulation of this disease process. [48] Blood lipids are primarily

influenced by nutrition, body weight, physical activity, stress, medications and genetic factors. Stress increases blood lipids by increasing hepatic lipoprotein lipase activity which is caused by a heightened sympathetic neuronal response during periods of acute stress. [48] Levels of free fatty acids and total cholesterol usually rise following acute and/or chronic stress. [48-50]

Stress induced dyslipidemia:

During acute stress, there is usually a rapid but transient increase in concentrations of total cholesterol, LDL, apoprotein B, triglycerides, and free fatty acids. This increase persists as long as the stressor is sustained. In chronic stress, it has been shown in different studies that dyslipidemia is sustained and may persist even after the stressor. [48-50]

Prolonged changes in lipid metabolism are induced by chronic stress. These can result in cardiovascular diseases like atherosclerosis, coronary heart disease, and stroke. According to studies conducted by Black PH in 2003 [50] stressful modern lifestyle exerts a strong influence on lipid metabolism. Stressful events may transform adaptive responses to pathophysiological changes. Acute increases in blood lipids are necessary to maintain homeostasis to survive and adapt to the stressor. [50]

In patients with depressive and anxiety disorders elevated basal levels of cortisol concentrations and lower circadian cortisol variability may lead to dyslipidemia. [48] In a study conducted by Veen G et al. patients presented with hypercortisolism. These subjects also had increased serum levels of total cholesterol, LDL, and triglycerides and decreased serum levels of HDL. [48] Depressive and anxiety disorders are usually associated with an increased risk of cardiovascular diseases. Chronic stress may induce hypothalamus-pituitary-adrenal (HPA)-axis perturbations. This may subsequently induce atherogenic lipoprotein profiles and increase in adiposity. The aim of the study was to establish relationship between basal salivary cortisol levels and serum lipids and

adiposity in patients having psychiatric problems. Patients demonstrated a higher mean AUC (cortisol) as compared to healthy controls. Both cortisol parameters were independently associated with dyslipidemia in patients after adjustment for age, alcohol use, and smoking habits.

Yoo H et al. in 2011 [49] in Iowa observed showed higher prevalence of hypercholesterolemia in stressed female law enforcement officers. The aim of the study was to assess the levels of stress and the prevalence of cardiovascular disease (CVD) risk factors in female law enforcement officers (LEOs). Self-reported data was obtained. These included job-related stress and CVD risk factors. Female LEOs had more stress scores (perceived stress, $p < 0.01$), more job-related stress (job strain, vital exhaustion and effort-reward imbalance, $p < 0.01$). They had similar social support (social provision scale, $p = 0.412$) as the male LEOs. Female LEOs had a significantly higher prevalence of hypercholesterolemia than the general Iowa female population ($p < 0.01$). Stress was the most commonly cited contributor to their perceived CVD risk. Female LEOs who felt that being either a LEO (67.7%) or a female LEO (41.5%) contributed to their risk for chronic diseases. They perceived higher stress. There was also a higher prevalence of overweight and obesity among LEOs who perceived higher stress as compared to than female LEOs who felt differently. Increase in perceived stress worsened lipid profile, blood sugar levels, body fat in female LEOs. Female LEOs demonstrated higher stress levels as compared to male counterparts. [49]

The negative effects of sustained stress-induced dyslipidemia are usually related to a bidirectional relationship between stress hormones and insulin. Sympathetic stimulation during stress causes catecholamines release. Catecholamines directly stimulate free fatty acid and glycerol secretion in the bloodstream from fat depots, a process that may result from increased blood flow

through adipose tissue or from adipose- $\beta 2$ adrenoceptor stimulation following sympathetic stimulation. Stress-induced rise in glucocorticoid concentration may exert a permissive effect on these lipolytic actions of catecholamines. [49-50]

Insulin regulates triglyceride synthesis and hepatic VLDL production. Insulin resistance results in unregulated triglyceride synthesis and VLDL production and triglycerides are secreted by the liver in large quantities within the VLDL particles. Both catecholamines and glucocorticoids antagonize the actions of insulin, contributing to insulin resistance. [48-50]

Cortisol induces apoprotein B (apo B) secretion from the liver in the proportion of one molecule apo B per VLDL particle. This action thereby increases the VLDL concentrations in the bloodstream. VLDL particle is usually metabolized to intermediate-density lipoprotein (IDL) or LDL. Thus the action of the cortisol that stimulates apo B secretion also results in increased LDL levels. Stress-induced insulin resistance causes high levels of glucocorticoids to suppress the hepatic LDL receptors and delay LDL clearance. [48-51]

Perilipin, coats the surface of lipid droplets. This helps to restrict lipase access to the triglyceride core within the droplet. Perilipin may suffer phosphorylation and down-regulation by glucocorticoid action. This facilitates the lipolysis of triglycerides in fatty acids and glycerol. The result may set off a vicious cycle, leading to more and more triglycerides being produced by the liver and secreted in VLDL particles. [48-51]

Norepinephrine and cortisol inhibit lipoprotein lipase activity. This may lead to diminished triglyceride clearance, decrease in HDL concentration, and increase in VLDL, IDL, and LDL concentrations in the bloodstream. Norepinephrine also diminishes hepatic triglyceride lipase activity. This in turn promotes high concentrations of lipoproteins rich in triglyceride in the blood. [48-51]

In stress-induced dyslipidemia, changes in food ingestion need also to be

taken care of. During acute stress, there is transient dyslipidemia and food intake inhibition. These are mediated by β -adrenergic activation and increased hypothalamic corticotrophin releasing hormone (CRH) levels which act as catabolic signals. Chronic activation of the hypothalamic-pituitary-adrenal axis has been associated with overeating and obesity. [48-51]

Changes in sleep-wake cycles are associated with stress. These result in sleep loss, and induce decreased leptin levels, increased Ghrelin levels, increased hunger and appetite, as cited by Pejovic S et al. in 2010. [51]

Stress, dyslipidemia and atherosclerosis: Putative mechanisms:

Dyslipidemia is a major underlying cause of the development of atherosclerosis. Atherosclerosis is an inflammatory process. [52] Stress-induced atherogenic lipid profile potentiates the effects of dietary and genetic factors responsible for atherogenesis. Stress has long been recognized as a major risk factor for atherosclerosis. [52-54]

Though there exists a definite association between dyslipidemia and atherosclerosis, many individuals with low serum lipid concentration develop severe atherosclerotic lesions. Some individuals develop far more severe atherosclerosis than would be expected on the basis of a modest elevation of serum lipids. In these cases, other effects of stress, not related specifically to dyslipidemia, may be involved in development of atherogenesis. [53-55]

The atherogenic effects of stress induce changes in nitric oxide (NO) levels; cytokine production; vascular smooth muscle mitogenesis; development of insulin resistance; increased neuropeptide Y (NPY) actions and modulation of the renin-angiotensin system activity. These effects may be directly and indirectly related to development of stress-induced dyslipidemia. [52-55]

The healthy endothelium provides a smooth barrier. This limits the activation of proinflammatory markers; blocks the transfer of Apo-B 100 (containing atherogenic lipid particles) into subendothelial space. It also inhibits the release of chemokines and cytokines; prevents platelet and monocyte adhesion to the vascular endothelium. [52-55]

A high amount of NO is usually produced by endothelial nitric oxide synthase (eNOS). It is a vasodilator substance. It has got antithrombotic properties. It is an inhibitor of smooth muscle cell proliferation. It also prevents leukocyte- and monocyte-adhesion. Decrease in NO bioavailability is a key feature for development of endothelial dysfunction. This results in lower responses to vasodilator agents, and represents an early stage of atherosclerosis. Endothelial dysfunction may significantly contribute to the development and progression of atherosclerosis in the following way: favoring coagulation; inflammatory cell adhesion; imbalance between vasoconstrictor and vasodilator responses; increasing transendothelial transport of atherogenic particles. [52-55]

Stress-induced rise of glucocorticoid levels usually reduces the expression of guanosine triphosphate cyclohydrolase messenger ribonucleic acid (mRNA). Guanosine triphosphate cyclohydrolase messenger ribonucleic acid is necessary for tetrahydrobiopterin cofactor (BH4) synthesis. Tetrahydrobiopterin cofactor stabilizes eNOS. If BH4 levels decrease, endothelial eNOS becomes uncoupled. As a result, transfers electrons to molecular oxygen generating superoxide anions. Superoxide anions react avidly with NO to form peroxynitrites, resulting in diminished NO bioavailability. This mechanism favors the traffic of oxidized lipids across the endothelium. High LDL levels induced by stress also decrease eNOS mRNA expression. [55-57]

Chronic elevations of cholesterol in the bloodstream are usually associated with

impaired endothelium-dependent NO production. This is due to increased interaction between caveolin and eNOS. Caveolin proteins are expressed in majority of cell types which play a role in development of atherogenesis. These include endothelial cells, macrophages, and smooth muscle cells. High levels of LDL cholesterol also increase the caveolin concentration in endothelial cells; strengthen the caveolin-eNOS complex; reduce the interaction between Ca^{2+} - calmodulin and eNOS. All these effects decrease eNOS translocation from caveolin to the cytoplasm and subsequently diminish NO production. Lipid peroxidation induced by stress impairs nitric oxide production (NO); stimulates inflammatory response; increases the traffic of inflammatory molecules and oxidized LDL to sub-endothelial space. All the above factor leads to vascular endothelial dysfunction. [53-57]

Insulin resistance also enhances the atherogenic effects of stress. Insulin stimulates NO production by the vascular endothelium. During chronic stress there is development of cortisol induced insulin resistance. Insulin resistance is usually associated with inhibition of the phosphatidylinositol 3-kinase pathway. There is over-stimulation of the phosphatidylinositol 3-kinase pathway. This reduces eNOS activity. It also accentuates free fatty acid-evoked oxidative stress. All these effects decrease NO bioavailability and promote an imbalance between vasoconstriction and vasodilation in vascular endothelium. This imbalance in responses of vascular endothelium predisposes the individual to atherosclerosis and arterial hypertension. Insulin resistance also increases the reactive oxygen species, and reduces eNOS activity. [57-59]

Morphological changes in blood vessels are usually associated with atherosclerosis. The increase in intima media thickness (IMT) in the carotid artery has long been used as a marker of target organ damage in human hypertension. [59] Dyslipidemia induced by hyper caloric diet

alone, did not promote morphological or functional changes in the thoracic aorta; or insulin resistance. This is an additional evidence of the role of stress in development of atherosclerosis.

NPY (Neuropeptide Y), is an orexiogenic peptide hormone. It may also be involved in the atherogenic effects of stress. Some stressors such as cold and aggression increase the release of NPY from sympathetic neurons. The peripheral actions of NPY are stimulatory. The peptide synergizes with glucocorticoids and catecholamines to potentiate the stress responses. It causes prolonged vasoconstriction thus potentiating the effect of norepinephrine. It further induces hyperlipidemia, and vascular remodeling by smooth muscle cell proliferation. In addition, it stimulates monocyte migration and activation and thus contributes to atherogenesis. NPY upregulates Y2 receptors in a glucocorticoid-dependent manner in abdominal fat. Consequently, there is development of abdominal obesity; hyperinsulinemia; dyslipidemia. In blood vessels, Y1 and Y5 activation of receptor also promotes pro-atherogenic responses. [60-61]

The high level of catecholamines induced by stress usually stimulates endothelial permeability to the traffic of oxidized LDL. Once these are trapped in the endothelium of an artery, LDL can undergo progressive oxidation. It may cross the endothelial barrier, and be internalized by macrophages expressing scavenger receptors. This leads to lipid peroxide formation and accumulation of cholesterol esters and culminating in foam cells formation. [60-61] Oxidized LDL particles upregulate the expression of adhesion molecules and secretion of chemokines. These contribute to the recruitment of circulating monocytes and leukocytes. [62-63] One of the major initial steps in the formation of atherosclerosis is the adhesion of monocytes to the vascular endothelium. Their entry into sub-endothelial space is followed by their differentiation into

macrophages. [63] These cells are also responsible for uptake of LDL and other particles, and thereby starting the atherogenesis process. [63] The macrophages in the endothelial space also have VLDL receptors. These bind the apolipoprotein (apo) E-containing lipoproteins, which include VLDL, intermediate density lipoprotein, β -migrating VLDL. The LDL-receptor-related proteins in macrophages are also capable of binding apo E-containing lipoproteins, lipoprotein lipase, and lipoprotein lipase-triglyceride-rich lipoprotein complex. [64] All these factors lead to the sequence in the development of atherosclerosis.

Activation of the renin-angiotensin system (RAS) by stress also plays an important role in the pathogenesis of endothelial dysfunction, hypertension and atherosclerosis. Lipid accumulation in blood vessels enhances the expression of RAS components. These in turn stimulates accumulation of oxidized LDL in blood vessels. [61] Activation of the angiotensin II-type 1 receptor (AT1R) may lead to vasoconstriction and neurohumoral activation. It is usually associated with reduced NO bioavailability; vascular cell apoptosis; increased oxidized LDL receptor expression; and proinflammatory cytokine production. [63-64]

LDL-cholesterol can accumulate in vascular smooth muscle cells. This effect is mediated via AT1R. Angiotensin II increases LDL uptake by arterial wall macrophages. Angiotensin II binds LDL. The angiotensin II-modified LDL is taken up by macrophages via scavenger receptors. These lead to cellular cholesterol accumulation. In atherogenic dyslipidemia, hypercholesterolemia increases AT1R density and its functional responsiveness to vasoconstrictors. The administration of statins reduces AT1R expression and deregulates its functions. [63-64]

The localization of angiotensin-converting enzyme in atherosclerotic lesions suggests an evidence of the capacity for local generation of angiotensin II and

proinflammatory substances. [63] Hypercholesterolemia increases plasma angiotensinogen and angiotensin peptide production. [63] AT1R antagonism improves hypercholesterolemia-associated endothelial dysfunction. This results in an anti-atherosclerotic effect. [64]

Dyslipidemia induced by stress is an important part of the body's response to cope with stressors. The increase in blood lipids induced by stress is adaptive and usually returns to normal levels when the stressor ends. But, when the stressor is maintained over a prolonged period, the dyslipidemia induced by stress persists. This may have deleterious effects and contribute to the development of insulin resistance, obesity, hypertension and atherosclerosis. [63-64]

Modern man no longer faces the epidemic of plague but stress related diseases are becoming number one killer. In the modern society stress is universal and relevant to all. A thorough understanding of stress management techniques is essential. This may promote prevention of stress related disease and enhance health. Stress management techniques needs to be incorporated into all levels of prevention. The need of different populations in different settings should be addressed while implementing these strategies. [1]

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