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The Neuropsychiatric Role of Platelets: Insights into Anxiety and Depression

Kalpna Verma[1], Ram KrishnaVerma[2]

[1]Department of Biochemistry, Dr. Rammanohar Lohia Avadh University, Ayodhya-224001, India

[2]Department of Microbiology, Kamla Nehru Institute of Physical and Social Science, Sultanpur- 228118, India

Abstract: ***Anxiety disorders are among the most prevalent mental illnesses, and their incidence is rising globally. The size, volume, and functions of platelets may vary because of generalized anxiety disorder, and mental stress makes platelets more aggregable. An increase in platelet volume and activity is often brought on by stress and anxiety via a variety of mechanisms. In individuals with a generalized anxiety disorder (GAD), the alterations in platelet indices may thereby increase their chance of developing thrombotic disorders in the future. Since people with generalized anxiety disorder have much greater mean platelet volumes, platelet distribution widths, and platelet crits than healthy adults, it might be inferred that they may be more susceptible to thrombotic disorders. In this review, we focused on the prevalence of anxiety and depression in teenagers and the role of platelets in anxiety and depression.***

Keywords: Mental stress, Platelets, Platelet aggregation, Serotonin, β-thromboglobulin

1. Introduction

The ancient Greeks were the first to speculate that negative emotions can contribute to the development of disease in the body [1]. Prospective epidemiological research using psychometrically sound measures of emotional dispositions provides substantial empirical data at present. Depressive, anxious, angry, and hostile states are some of the negative affective disorders that have been associated with atherosclerosis and unfavorable cardiac events. Depressive symptoms have been linked to an increased risk of developing CHD and a worse prognosis for those who already have the condition. Clinically depressed people had a greater than 2.5-fold higher risk of myocardial infarction or coronary mortality than the general population, according to a meta-analysis by Rugulies on the correlation between depression and coronary artery disease [2].

When unpleasant emotions had a negative effect on behavioral factors including smoking, eating, exercise, and adherence to medical treatment, the risk of cardiovascular morbidity and mortality rise. Moreover, molecular processes crucial to the emergence and progression of CHD seem to be directly impacted by psychological variables [3]. Cortisol production is greater, the sympathetic nervous system is activated more, and the plasma catecholamine levels are higher in those who are depressed and hostile. In addition to heightened levels of inflammatory cytokines and platelet reactivity, depression is linked to hypertension, endothelial dysfunction, and several other conditions. A lot of attention has been paid lately to the connection between melancholy and platelet function [4].

Particularly in the absorption, storage, and metabolism of serotonin, platelets and neuronal monoamine systems of the central nervous system exhibit numerous molecular similarities. The platelet and brain serotonin transporters are encoded by the same gene, and they are parallels between the 5-HT2A receptors in platelets and serotonergic neurons in the brain. It is not unexpected that serotonin-mediated platelet activation has been identified as a fundamental pathogenic relationship between depression and CHD, providing the prominent role that platelets play in both acute and chronic coronary syndromes [5]. Serotonin and other circulating agonists like catecholamines interact with several receptors in the platelet membrane to activate the platelets. Specific 5HT2A receptors have been discovered to be involved in platelet aggregation, and serotonin (5HT) is regarded as a key player in psychopathology and psychopharmacology.

When compared to healthy, non-depressive people, depressed patients have shown greater 5HT-mediated platelet reactivity. As an alternative, catecholamines stimulate the α-2 receptors on platelets to activate them. Because the two agonists work in distinct ways, there is a synergistic impact between 5HT and epinephrine on platelets. Anxiety patients have higher levels of autonomic activity and circulating catecholamines, which may cause their platelets to become activated. Higher levels of β-thrombomodulin, platelet factor 4, and P-selectin have been seen in individuals with depression, according to many investigations. Additionally, it has been shown that depressed individuals have greater platelet glycoprotein IIb/IIIa receptor activation as well as enhanced serotonin-mediated platelet reactivity. However, it's crucial to be aware that researchers studying the connection between platelet and depression reactivity have produced mixed findings, with some studies demonstrating no change in platelet reactivity between non-depressed and depressed people. These contradictory results can simply be the consequence of methodological disagreements, or they might rather represent real physiological variations across various patient groups [6].

While platelet function in patients with depression has undergone extensive examination, platelet reactivity in patients with other negative affective diseases has gotten comparatively less attention. Epinephrine and different serotonin doses were used to stimulate platelets. Optical aggregometry was used to evaluate platelet aggregation, and flow cytometry was used to determine platelet surface receptor activation.

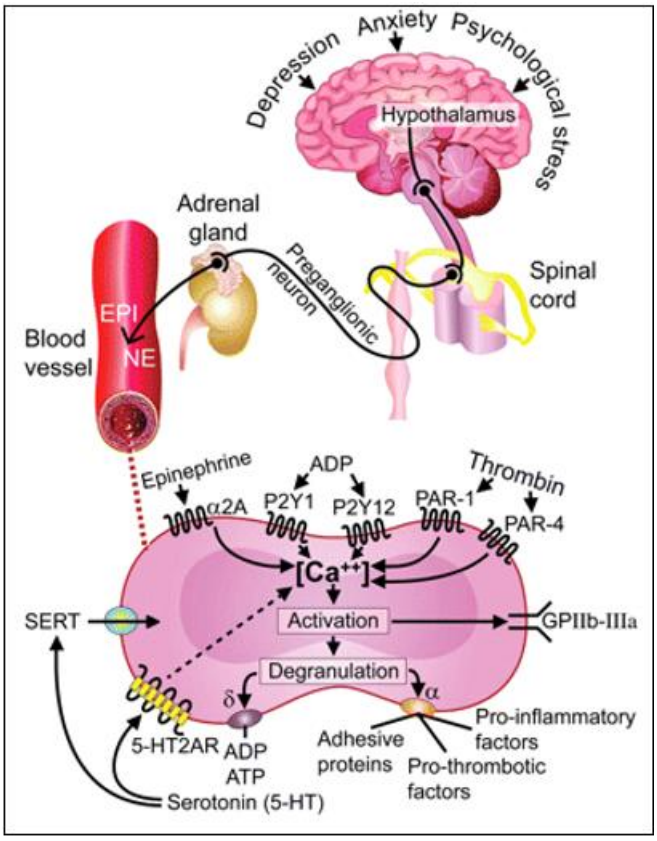

Figure 1: Depicts the correlation between anxiety, depression, and platelets

2. Anxiety and Depression

The notions of anxiety and depression, are both parallels and distinct. In the elderly, anxiety and depressive disorders are quite common, often manifest as comorbid disorders, and both have negative outcomes including decreased quality of life and increased mortality. These two conditions are commonly comorbid and are together referred to as internalizing disorders. According to data from the Substance Major depressive disorder was expected to impact 7.1% of adults and 13.3% of adolescents in 2017 for 12 months, according to the Abuse and Mental Health Services Administration [7].

Both severe depression and anxiety disorders can emerge at any stage of life, with anxiety disorders commonly beginning in preadolescence and early adolescence and major depression often emerging throughout adolescence and early to mid-adulthood (16–18 years). Additionally, subthreshold feelings of anxiety and sadness are widespread and substantial, seriously interfering with everyday life [8]. Table 1 depicts various kinds of anxiety disorders.

Table1: Lifetime prevalence of different anxiety disorders

Anxiety Disorder	Lifetime Prevalence	Symptoms
Agoraphobia	1.3%	Fear of circumstances or locations where escaping would be difficult or humiliating.
Specific phobias	12.5%	Intense, irritational fears of specific objects or situations
Panic Disorder	4.7%	Repeatedly occurring panic attacks with no identifiable stressor
Social anxiety disorder	12.1%	Fear of engaging in or performing in front of others
Generalized -anxiety disorder	5.7%	Chronic and excessive worrying about individuals or events

a) Cognitive Models of Anxiety and Depression

Both anxiety and depression have a shared sense of danger, according to cognitive theories of both disorders. In the case of anxiety, it seems that the danger is hypothetical, with the possibility that one's capacity to cope with the outside world, happiness, or self-worth may be threatened [9]. But in depressed responses, the harm to one's capacity to cope, happiness, or self-worth is seen as either immediate or inevitable, as has already happened. The one emotional pattern, anxiety, is future-focused and predicts danger, but depressive reactions are either linked to impending or past events that have a direct impact on self-esteem, and so on. This is a key distinction between anxiety and depression [10].

b) Brain parts involved in anxiety and depression

When the amygdala, a region of the brain, detects danger, anxiety follows. When it detects danger, real or imagined, the body is flooded with hormones adrenaline and other chemicals that make the body powerful, quick, and strong [11]. The fight-or-flight reflex, which has kept us alive for countless years, gets activated. Obsessive-Compulsive Disorder (OCD), a phobia, or generalized anxiety disorder (GAD) are the most common diagnoses for children with anxiety problems. Mental health professionals are discovering that these diseases, which were long regarded to be "adult" illnesses, are becoming more common among youngsters under the age of eighteen. A nervous brain is a robust, healthy brain that leans a bit too much toward overprotection. It will probably detect danger and press the emergency button "just in case." One of the worst aspects of anxiety is how it frequently strikes without notice and causes, forcing an unprepared body into unnecessary fight or flight [12].

Any circumstance that is unfamiliar, strange, challenging, or unpleasant might be a hazard to a youngster who suffers from anxiety. Their bodies are immediately and automatically primed for fight or flight by the fight or flight response, which causes neurochemicals to flood throughout their bodies. The left and right hemispheres of the brain make up the whole structure. A group of fibers known as the corpus callosum connects the two sides. Along these fibers, right and left-brain communication take place, but sometimes, such as during worry, the signals don't flow easily. Several brain regions play important roles in the generation of fear and anxiety [13]. Scientists have shown that the hippocampus and the amygdala play important roles in most anxiety disorders using brain imaging technologies and neurochemical methods. The almond-shaped amygdala,

a structure deep within the brain, is considered to act as a communication channel between the parts of the brain in charge of decoding and interpreting sensory data. It might send a warning to other brain regions, triggering a fear or anxiety response [14].

The emotional memories of the central amygdala could have a role in anxiety disorders, especially those involving phobias of a particular kind, such as aversions to flying, dogs, and spiders. The area of the brain that records dangerous experiences as memories is called the hippocampus. According to studies, the hippocampus is smaller in certain persons who have experienced child maltreatment or who have been in battle [15]. The origin of this shrinkage and its impact on flashbacks, deficiencies in the explicit recall, and fragmented recollections of the traumatic incident will be the subject of further research. Additionally, specific brain regions take on a dominating role and influence behavior.

This is an indication of a strong, healthy brain going into survival mode, but it hurts when it occurs often or needlessly. Responses become stiff; what happens in risky conditions also happens in non-threatening ones. For instance, the left brain enjoys logic and utilizes words to express the experience in a concrete, logical manner [16]. The right brain has a more emotional and big-picture emphasis on what the incident suggests. It is heavily reliant on memories, emotions, and images, and is strongly impacted by physiological sensations and impulses from the lower brain, which is the main source of concern. The feelings are overwhelming, and if the left brain isn't completely activated, they could not make sense. There must be a balance between the right and left to maintain everything in order [17].

c) Anxiety and risk assessment

Anxiety is a condition of "action readiness" connected to unanticipated or uncontrolled unpleasant stimuli [18]. The term "readiness" in this context refers to being ready to act when the right circumstances (affordances) present themselves. Fanselow and colleagues refer to this circumstance as the "pre-encounter environment," in which case behavioral modifications are done under the umbrella category of "risk assessment." Risk assessment is a group of modifications that is engaged in the detection and interpretation of threat stimuli and the environment in which it happens [19]. To identify and/or react to prospective predators, animals will divert their focus from current motivated activity. Animals adopt a baseline of "apprehension" when there is a chance of harm, which leads them to choose watchful behaviors. In these circumstances, animals also tend to "overestimate" the real amount of danger; this "cognitive bias" causes animals to limit ongoing activities and escape, hide, or freeze if any indicator of risk is seen. Animals often withdraw to protective regions, engage in behaviors like thigmotaxis ("wall hugging") and scototaxis ("dark preference"), and construct "home bases" to which they repeatedly return after exploring the world, depending on the available environmental affordances [20].

According to Montgomery's theory, unfamiliar settings arouse both anxiety and the desire to explore, leading to a struggle between approaching and avoiding. It's important to note that novelty presents a possible danger scenario, and exploratory behavior is modified appropriately [21]. This is investigated in many behavioral models of anxiety, where forced novelty exposure results in risk-taking behavior and changes to exploration. Anxiolytic medications boost exploratory activity in wholly unfamiliar surroundings, especially unpleasant devices (such as the open arms of an elevated plus-maze, the illuminated chamber of a light or dark box, or the middle of an open field).

Table 2. Anxiety and risk assessment

Psychosocial	Unemployment, a lack of social support, and a decline in socioeconomic position.
Demographic	Male, widowed, divorced
Behavioral dimensions	Impulsivity, hostility, severe anxiety, panic attacks, and a history of suicidal ideation
Trauma	Traumatic incidents, neglect, and sexual/physical abuse
Genetic and Familial	Suicide, mental illness, or abuse in the family history.
Cognitive Dimensions	Thought constriction, polarized thinking,

3. Anxiety and depression in teenagers

Anxiety is a state of unease, unease, dread, or anxiety. Some fears and concerns are valid, such as anxiety for a loved one or anxiety related to an upcoming quiz, test, or another exam. Problem anxiety prevents the patient from sleeping or doing other daily tasks. Amazingly, teens are more likely than adults to experience irritation as a sign of several emotional issues, including anxiety [22].

In his work, Gullotta noted that when anxiety is employed to react to a stressful circumstance, it may be beneficial. For instance, when an adolescent is getting ready for an exam, a little worry motivates them to study hard and achieve well [23]. Anxiety in adolescents may also isolate them from their friends, making them less likely to participate in activities that might help them relax and deal with their problems and performance in school impacted by fear. Twenty percent of young individuals will struggle with the anxiety of some kind. Additionally, 5% of children and adolescents suffer from these diseases, which are more frequent in females than in boys and more common in adolescents than in children. Additionally, 13% of all young people have an anxiety disorder, according to research. Depressed teenagers may exhibit introversion or rebellious behavior during the prepubescent era.

The feeling of unhappiness or distress is referred to as a depressed mood. Depression can cause negative emotions such as sadness, helplessness, weakness, disappointment, irritability, despair, and hopelessness. Because they lack courage in their actions, many depressed people may find it difficult to perform well in school [24]. They might think that their performance falls short of the bar set for it. As a result, they are perpetually disappointed and hopeless. They have a negative outlook on life and believe they are failures. Too many serious issues, such as receiving subpar grades, can be attributed to this issue in their academic lives.

4. Role of Platelets in anxiety

The hypothalamic-pituitary-adrenal (HPA) axis goes into overdrive in response to stress, most likely via neurotransmission mediated by a corticotrophin-releasing factor. The serotonergic and sympathetic nervous systems in the brain are functionally altered, therefore. Stress in the mind triggers the inflammatory response system, which keeps the HPA axis hyperactive [25]. Young males in good health had their platelet bioactivity PF-4 and -TG measured in response to mental stress activities like mental arithmetic or the cold pressor test. Stress activities had a substantial impact, rising PF-4 and -TG levels were seen, therefore. The effects of acute psychological stress tasks on the development of PLA in healthy persons were the subject of two investigations. To examine the habituation effect among full-time workers who were evaluated twice in four weeks, Hamer et al. adopted a longitudinal approach [26]. According to the socioeconomic class of the males, Hamer and Steptoe assessed PLA development brought on by acute mental stress and recuperation. Participants' perceptions of the test's difficulty, their performance, their controllability, and their sensations of stress were all examined in both experiments.

Table 1: Platelet granules and their products.

Platelet granules	Alpha-granules	Dense granule	Lysosomal granule
Platelet products	Albumin Fibrinogen Fibronectin Vitronectin Osteonectin Calcitonin Von Willebrand Factor Von Willebrand antigen II Platelet factor 4 Thrombospondin IgG, IgA, IgM C1 inhibitor Plasminogen Plasminogen activator inhibitor-1 Platelet-derived collagenase inhibitor High molecular weight kininogen Protein S α2-Antitrypsin α2-Macroglobulin α2-Antiplasmin Multimerin Platelet basic protein β-Thromboglobulin Histidine-rich glycoprotein Connective tissue- activating protein III Neutrophil-activating protein II Platelet-derived growth factor Coagulation factor V Coagulation factor VIII Substance P Vasoactive intestinal peptide >300 other proteins	Serotonin Histamine ATP ADP Calcium Magnesium Pyrophosphate	Cathepsin D Cathepsin E Carboxypeptidase A Carboxypeptidase B Proline carboxypeptidase β-*N*-acetyl-d-hexosaminidase β-d-glucuronidase β-d-galactosidase α-d-mannosidase α-l arabinofuranosidase α-d-galactosidase α-l-fucosidase β-d-fucosidase β-d-glucosidase α-d-glucosidase Acid phosphatase Angiotensinogen Arylsulfatase

Platelet-monocyte aggregates and platelet-neutrophil aggregates, two PLA subset forms, were assessed by FACS. Mental stress exercises were shown to have an influence on PLA production that was considerably rising. Regarding the stress recovery time, PLA peaked 30 minutes after the stressor and returned to baseline 75 minutes later. PLA's ability to evaluate stress reactivity was not significantly influenced by socioeconomic level, while lower socioeconomic status was linked to greater baseline PLA. There was no habituation effect seen. A useful methodological examination into a potential habituation effect in stressful situations is provided by Hamer et al. for Up to 75 minutes to investigate platelet activation in the post-stress phase, which seems to be a suitable time frame for healthy males. Both researchers gathered data from young, healthy guys [27,28].

Platelet reactivity in old people was the subject of four distinct research by Aschbacher et al. A cross-sectional methodology was used to examine the effects of extra acute mental stress in conjunction with depressed and anxious symptoms or hormone replacement treatment in dementia careers, which is a well-established paradigm of chronic mental stress. Further, two long-term studies were done to

consider the effects of acute mental stress in a senior population without caregiver stress and in dementia careers paired with continuous depressive symptoms [29].

5. Role of Platelets in Depression

Because platelets and the neuronal monoamine system in the central nervous system have many similarities, the association between depression and platelet function has received attention [30]. Serotonin and noradrenergic systems are the primary sites of platelet abnormalities in depressed people. The density of noradrenergic receptors changes together with the intake, storage, and metabolism of serotonin [31]. Since serotonin primarily controls happy emotions and mood in a healthy brain, the balance of serotonin metabolism can play a significant role in the genesis of depression. Interestingly, elevated platelet reactivity is also connected to depression. The dense granules of platelets house more than 99% of the body's serotonin. Furthermore, antidepressants may protect the vascular system by splitting up blood clots [32].

6. Molecular signaling of platelets and serotonin

Serotonin, also known as 5-hydroxytryptamine (5-HT), is a monoamine neurotransmitter that modulates the brain's ability to process central information [33]. Numerous physiological, behavioral, and cognitive processes, including memory, sleep, emotions, food, and temperature control, are affected. Additionally, 5-hydroxytryptamine has long been linked to the pathophysiology of mental diseases including addiction, anxiety, and obsessive-compulsive disorder (OCD) [34]. The bulk of the body's total 5-hydroxytryptamine is generated and stored peripherally in the enterochromaffin cells of the digestive tract, whereas only a small amount is produced in the serotonergic neurons of the CNS and released into synapses. The membrane of serotonergic axon terminals contains a protein called a serotonin transporter (SERT) [35].

When 5-hydroxytryptamine is released into the bloodstream from enterochromaffin cells in the periphery, platelets quickly absorb it via the Serotonin transporter and store it in platelet-dense granules. The serotonin transporter is thought to have a role in the genesis of neuropsychiatric diseases such as major depressive disorder, anxiety-related disorders, and OCD by regulating the concentration of free active 5-hydroxytryptamine in the synaptic cleft of the central nervous system. The fact that selective serotonin reuptake inhibitors are used as a first-line therapy option for the treatment of major depressive disorder and anxiety disorders, as well as the potential to treat other psychiatric conditions like obsessive-compulsive disorder, shows that SERT serves as a biological target for clinically effective antidepressants. These factors have led to SERT being a study focus on the world of psychopharmacology during the last several decades. Among the several organs that produce SERT, platelets exhibit some serotonergic responses comparable to those of neurons, despite clear distinctions in the origins of 5-hydroxytryptamine and 5-hydroxytryptamine receptors.

Since the same single gene expresses the Serotonin transporter protein in neurons and platelets, it has been discovered that mutations that change its expression have an equivalent effect on function in human platelets and the brain [36]. Second, human platelets and the brain express SERT with the same amino acid sequence and pharmacological sensitivity. Third, 5-hydroxytryptamine absorption by Serotonin transporter, metabolism, storage, and release processes are identical in serotonergic neurons and platelets. Fourth, comparable to the one in neurons, the platelet uptake system has a relatively high affinity for 5-hydroxytryptamine and is blocked by the same substances that block the neuronal uptake system [37]. Additionally, it is simple and convenient to regularly collect blood samples from live individuals, and platelets may be easily isolated and purified from other blood cells [38]. It has been shown that SSRIs or psychostimulants that block SERT activity alter 5-hydroxytryptamine levels in neurons and platelets comparably. After many weeks of therapy, SSRIs were shown to reduce platelet 5-hydroxytryptamine concentration by 80–90% in human trials [39-41].

7. Role of serotonin in depression and anxiety:

Serotonin (5-hydroxytryptamine, 5-HT) has long been acknowledged as a crucial factor in the regulation of mood and anxiety and is closely linked to the genesis of major depressive illness, according to Robson et al., (2017) [42]. Although 5-HT is better known for its functions inside the central nervous system (CNS), it is also known to influence several important components of immune system function that may help MDD develop [43]. Numerous studies have shown a relationship between MDD and changes in immune system functionality and inflammation levels. Peripheral immunological activation alters the function and/or expression of several 5-HT signaling components linked to depressive-like phenotypes, providing evidence for this association. It is still unclear how the immune system uses 5-HT to influence CNS function and, ultimately, behaviors associated with depression [44,45].

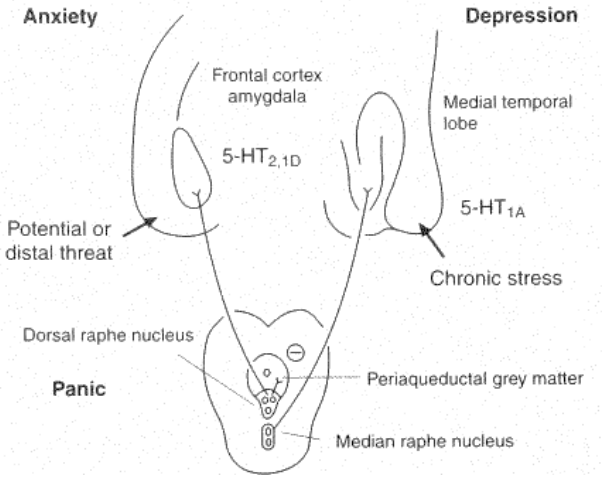

Figure 2: 5-HT signaling components

According to research by Deakin et al. (1998), anxiety and depressive disorders span a wide range, and each illness may be caused by unique genetic and neurobiological/ neurochemical causes [46]. Several medication classes may be used to treat various illnesses, and as would be predicted,

these treatments have a wide range of biochemical effects. Ironically, a variety of these diseases respond well to single-action selective serotonin reuptake inhibitors. Understanding the many ways that 5-HT changes the physiological coping mechanisms that become faulty in these illnesses, however, may help to reconcile the dilemma [47].

Table 3: Role of serotonin in anxiety and depression

Receptor	Action	Drug examples	Clinical Disorder
SERT (5-HT transporter)	Inhibitor	Fluoxetine, sertraline	Depression, panic disorder, social phobia
5-HT_{1A}	Partial agonist	Buspirone, ipsaperone	Anxiety, Depression
5-HT_{4}	Agonist	Cisapride	GI disorders
5-HT_{1D}	Agonist	Triptan	Migraine
5-HT_{3}	Antagonist	Ondansetron	Chemotherapy-induced emesis

8. Future Perspectives

Strong evidence suggests that increased platelet activity caused by mental stress occurs in healthy males [48]. The post-stress recovery phase should be the main topic of future studies, and it is also necessary to replicate the current findings. More research is needed on platelet activation in women, considering the potential role of female hormones. In this context, it is important to note that platelet studies should appropriately account for confounding factors related to lifestyle, nutrition, and medication. Also, important factors to consider are socioeconomic status and individual stress levels.

An ideal explanatory model has been developed using solid data on an older population (mean age 70), which allows for the analysis of the interactions between acute and chronic mental stress situations, mood symptoms, and platelet activation. Future research should explore the connection between stress-induced mood symptoms and platelet activation since depressed and anxious feelings were predicted for p-selectin reactivity [49].

Mental stress demonstrated consistently raised PLA levels in cardiovascular illness, although further study is needed on platelet activation after stress. These results suggest that this patient group may benefit clinically from effective psychosocial stress management. Females and people of various ethnic backgrounds who suffer from cardiovascular disease have less data on platelet stress reactivity [50].

Controversial findings come from the evaluation of circulating platelet activation chemicals in sera or plasma. This discovery is consistent with data gathered on depressed patients and under physical stress. Therefore, it has been recommended that the most sensitive method is the examination of platelet activation indicators by FACS, particularly the detection of PLA levels.

An effective tool for assessing numerous psychopathological symptoms of PTSD patients' platelets' serotonin content and MAO activity may be obtained. These demonstrate a relationship between serotonin levels and the lack of appetite in depressed individuals, as well as a relationship between suicidality and psychotic traits, but not a relationship with the disease itself [51]. The current investigations thoroughly screened for potential confounding factors by prior study data (smoking habits, seasonal variations, gender, and medication). It has been hotly debated in the past whether platelet serotonergic characteristics may serve as peripheral biomarkers.

9. Conclusion

Patients with anxiety and depression have higher levels of platelets and 5-HT, indicating a possible link to the development of these disorders. There are platelets in MS lesions, and studies have described their increased adhesiveness in this condition as well as other abnormalities, such as structural changes, upregulation of enzymes, and markers of platelet activation. As a result, the platelet is linked to various disease types and stages. Also anxiety and depression disorders demands high costs for both the affected person and society. The number of people in need of therapy is higher than the number of available therapists, therefore many depressed and anxious individuals get inadequate or no treatment at all. Therefore, it is crucial to support individuals in actively managing their health. Regular exercise may significantly enhance mental health, and the benefits of exercise can be increased when they are combined with cognitive behavioral theory.

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