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Is Anxious-Depression an Inflammatory State?

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Abstract

For several years, the literature has examined the association of depression and anxiety with inflammatory states such as atherosclerosis and cardiovascular disease, yet this association remains inconclusive. Several possible immune and endocrinological pathways have been postulated that associate depression and anxiety with inflammation and immune dysregulation. Anxiety and depression have usually been envisioned as two separate psychiatric conditions yet they share similar symptoms and are frequently encountered together among individuals. Individuals suffering from anxious-depression are more refractory to treatment and have been reported to have greater disability compared to individuals with anxiety or depression alone. With the current changes in the diagnostic manual for psychiatric disorders placing more emphasis on a dimensional approach for the diagnosis of psychiatric illnesses, the hypothesis presented is that anxious-depression should be considered as a chronic inflammatory phenomenon since it shares common physiopathological pathways and pharmacological treatments with inflammatory states. This hypothesis might help to investigate how different levels of inflammatory biomarkers could be correlated with symptoms of anxious-depression.

The Construct of Anxious-Depression

During the early 1990s the concept of mixed anxiety and depression was portrayed as an important condition, worthy of clinical attention, that was frequently found in primary care settings and did not meet full diagnostic criteria for major depression or an anxiety disorder; this diagnosis has been frequently referred as *anxious-depression*¹. Early studies in community samples found increased suffering, disability and exacerbation of chronic medical conditions among patients with anxious-depression¹. Similarly, subsyndromal anxiety and depressive states have been associated with loss of productivity and lack of adequate treatment^{2–4}. Anxious-depression has been a condition of interest in the updated version of the Diagnostic and Statistical Manual for Mental disorders (DSM) due to the high co-occurrence of symptoms of anxiety and depression observed in clinical settings⁵. Consensus from experts is that more research is needed for anxious-depression to meet test-retest reliability as a well established diagnosis^{6,7,8}.

In behavioral health, diagnoses are usually conceptualized within a dimensional or categorical approach. The dimensional approach to study anxious-depression has been suggested as having some advantages over the traditional categorical approach⁹. Traditional categorical approaches identify individuals suffering or not from a given behavioral health problem. The categorical approach has the disadvantage of not considering individuals

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below the established cutoff threshold, although some categorical classifications allow for a spectrum of continuity based on the severity of symptomatology, i.e. mild, moderate or severe. Individuals with subsyndromal classification of anxiety and depression states are usually not the focus of clinical attention^{2,4,10}. Individuals with anxious-depression are frequently seen in primary care clinics and are better captured when a dimensional diagnostic approach is used with severity of symptoms within the spectrum^{5,11}. A recent review of the literature found that the dimensional use of anxious-depression yields a more serious clinical presentation in which inflammatory markers could serve as direct measure of this commonly seeing condition in primary care settings^{12,13}.

Our group has started to study the dimensional construct of anxious-depression. Following this dimensional approach, our group showed preliminary data on 16,000 individuals participating in a large epidemiological study in which states of anxiety and depression cluster together in an anxious-depression spectrum (mild, moderate, severe)¹⁴. That spectrum-like disorder could be used as a single construct to study associations with chronic medical conditions resulting from pervasive inflammatory states such as diabetes, obesity, atherosclerosis and metabolic syndrome.

During the past two decades, there has been an increased interest in understanding the association between mood, anxiety symptoms and chronic medical conditions affected by inflammatory states such as atherosclerosis^{15,16}. Since studies have shown that depression is an independent risk factor for cardiovascular disease^{17–19}, in recent years, attention has shifted to anxiety disorders as a possible independent risk factor for inflammation and cardiovascular disease²⁰. Because depression and anxiety coexist¹, lessons learned from a number of studies looking at changes in depressive states have provided the ground work to study the association of anxious-depression states with atherosclerosis in which inflammation is considered to be the common biological pathway^{21–24}.

With the current need to integrate behavioral health in the primary care settings²⁵, it is reasonable to study anxious-depression and inflammation as a common chronic medical condition. Inflammation is considered to have a crucial role in the pathogenesis of affective states, atherosclerosis and metabolic disorders^{23,26,27}. Therefore, the main hypothesis is to consider anxious-depression as a chronic inflammatory state considering the overlapping biological processes and shared treatments encountered in anxious-depression, immunological states and inflammation.

Anxious-Depression as an Inflammatory Phenomenon

Immunological Evidence

Biologically, anxiety and depressive symptoms have been associated with changes in the hypothalamic-pituitary-adrenocortical (HPA) axis, autonomic nervous system tone, immune response, endothelial integrity, coagulation and vascular reactivity; all of these systems are crucial in the generation of a systemic inflammatory response^{15,20,21,28–30}. HPA axis dysregulation has been considered as the landmark biological connection between anxiety, depression, the central nervous system and systemic inflammatory response³¹. Hyperactivation of the HPA axis is associated with hypersecretion of corticotropin-releasing factor (CRF), a peptide that mediates endocrine, autonomic and behavioral responses to states of anxiety and depression³². Hyperactivation of CRF has been considered a novel biomarker for depression and anxiety due to their close association with systemic depression, anxiety, stress and inflammation³². Studies have reported that CRF may affect systemic inflammation via a peripheral paracrine effect similar to those observed in the HPA axis^{33,34}. In fact peripheral CRF acts on receptors of inflamed tissue similar to the

neuropeptide serotonin implicated in anxiety and depression as well as the novel Interleukin (IL)-1, a potent pro-inflammatory cytokine^{32,34,35}.

IL-1 is present in peripheral immune cells as well as glia and neurons. This inflammatory cytokine has been shown to have a critical role in decreasing hippocampal neurons responsible for the production of serotonin in response to inflammatory states³⁶. Furthermore, IL-1 has been shown to be closely associated with states of depression and inflammation³⁷. In summary, IL-1 is a novel systemic and neurologic biomarker that could explain how anxious-depression and inflammation are a similar phenomenon.

Although there are studies showing no association of mood states with inflammation^{38,39}, there is evidence that anxious-depression states are associated with increased activation of T-helper lymphocytes and increased levels of pro-inflammatory cytokines such as IL-6, IL-1, IL-2, IL-4, IL-10⁴⁰ as well as acute phase reactants such as C-reactive protein and tumor necrosis factor- α (TNF- α)^{28,41}. In a study performed in 38 medical students before and after an academic examination, investigators found that anxiety states are associated with increased levels of TNF- α , IL-6, IL-1 receptor antagonist (IL-1Ra), interferon gamma (IFN-gamma), IL-10 and IL-4⁴². These findings provide further evidence that the production of the pro-inflammatory cytokines and thus inflammatory states clinically manifest as anxiety and depressive states. Furthermore, dysfunction in the tissue plasminogen activation factor has been implicated in the exacerbation of inflammatory states such as atherosclerosis in which anxiety and depressive states are the main clinical manifestation^{10,21,43–45}.

The moderating effect of the proinflammatory cytokine indoleamine 2,3-dioxygenase (IDO) in reducing the availability of tryptophan for the synthesis of serotonin is another evidence of the commonality of anxiety and depression with inflammatory states. IDO is an inflammation-related enzyme, mainly expressed in antigen presenting cells that degrades tryptophan, a serotonin precursor, to kynurenine^{13,24}. Furthermore, recent studies in rodents found that inflammatory states created by injection of bacterial endotoxins increased the activity of IDO as measured by increased kynurenine/tryptophan quotient which is directly observed by exacerbation of depression and anxiety-like behaviors⁴⁶. Similarly, Maes and coworkers described increased activation of IDO during the acute inflammatory state of early puerperium observed in women. Maes et al. found increased symptoms of anxious-depression as the direct clinical manifestation of the inflammatory state of puerperium as measured by the direct activation of IDO⁴⁷. This further demonstrates the link not only at a preclinical but clinical level of anxious-depression with inflammatory states where the immune system is the common pathway.

To further corroborate the above mentioned evidence, investigators have reported that inflammation reduces the availability of the enzyme cofactor tetrahydrobiopterin which is crucial in the activities of tryptophan hydroxylase and tyrosine hydroxylase, both rate-limiting enzymes essential for the synthesis of serotonin, dopamine and norepinephrine. Deficit in these neuroamines is reflected in symptoms of anxious-depression^{48,49}.

Genetic Evidence

In addition to the shared immune and cytokine activity seen in inflammation and anxious-depression, authors have reported that there is an up-regulation of genes associated with the expression of inflammatory cytokines among individuals endorsing high scores of depression and anxiety states⁵⁰. Crucial genes expressed by leukocytes that have been associated with inflammation, cellular stress and mood states are STMN1, p16^{ink4a} as well as FOS, DUSP1, TERT and the IL-6 gene. Among these pool of genes, FOS and DUSP1 have been reported good candidates to responses to stress, inflammation and anxiety states^{50,51}. Teyssier and collaborators⁵⁰ found a strong association of the leukocyte

expression of the STMIN1 and p16^{ink4a} with high scores of anxiety symptoms among patients diagnosed with depression. This study postulates that genes transcripts implicated in anxiety, depression and inflammation are highly correlated with each other which provides good evidence supporting the theory that anxious-depression is a chronic inflammatory state.

Treatments for the Anxious-Depression Inflammatory State

Common treatments for anxiety, depression and inflammation further supports the hypothesis that anxious-depression is an inflammatory state. Several studies have demonstrated that antidepressants, which are the pharmacological treatment of choice for anxiety and depression, have anti-inflammatory properties^{52,53}. Several investigators demonstrated that infusing the commonly used selective serotonin reuptake inhibitor (SSRIs) antidepressants in whole blood produces a marked reduction in the pro-inflammatory cytokine interferon-gamma and increases the secretion of the anti-inflammatory cytokine IL-10⁵³⁻⁵⁵.

Chronic pain, a known chronic inflammatory condition, has traditionally been treated with different types of antidepressants such as tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), SSRIs, selective serotonin noradrenaline reuptake inhibitors (SNRIs) and norepinephrine reuptake inhibitors (NRIs)⁵⁶. Furthermore, fibromyalgia which by definition is a systemic non-specific inflammatory state has shown to respond well to SSRIs and TCAs⁵⁷.

Evidence shows that the administration of anti-TNF- agents such as etanercept reduces anxious-depression behaviors in animals. Researchers found that TNF- has well established role in inflammation but also a role in the modulation of anxious and depressive states providing a novel strategy to treat inflammatory conditions such as anxious-depression⁵⁸. Similarly, infliximab a known monoclonal antibody that targets TNF- has shown to reduce symptoms of anxious-depression among patients with high concentrations of the inflammatory marker C- reactive protein⁴⁸.

Clinical Implications

The biological evidence presented on how anxious-depression and inflammation share the same physiopathological process has important clinical implications. Studies have extensively documented that metabolic syndrome and cardiovascular disease predicted increase in anxiety and depressive symptoms among patients^{59,60}. Janszky et al. examined data from around 50,000 participants followed for an average of 37 years. The authors found that anxiety disorders were a significant predictor of chronic inflammation manifested as atherosclerosis and subsequent cardiovascular events^{20,61}. On the same note, a meta-analysis by Roest and collaborators found that anxiety symptoms predicted cardiovascular events 11 years after the onset of anxiety symptoms^{20,62}. To further validate the hypothesis that anxious-depression is an inflammatory state, a recent longitudinal study demonstrated over a 2 year period, that individuals with initial symptoms of anxiety and depression developed an increase in abdominal obesity and dyslipidemia⁶³. The common biological pathways between chronic inflammatory states such as obesity and affective disorders are considered critical areas of clinical research that have direct implication for the development of prevention and treatment programs⁶⁴.

Future Implications

For decades, the literature has emphasized the importance of addressing treatments for anxious-depression and chronic inflammation as one condition⁶⁵. Anxious-depression is a

proposed dimensional construct that could be used as a direct proxy measure of chronic inflammation. It is important to consider that the immune system has been described as the main regulator of inflammatory responses and mood states⁶⁶. The immune system could be an important mediator for the proposed chronic inflammatory state of anxious-depression. For example, biological markers of immune dysregulation could be used to determine the level of inflammation among individuals experiencing symptoms of anxious-depression. These same biological markers could be used to study the association of chronic inflammatory conditions such as obesity and atherosclerosis with different dimensional states of anxious-depressive symptoms.

The new DSM-5 emphasizes the need to better operationalize the concept of anxious-depression^{5,6}. The hypothesis postulated herein is that anxious-depression should not only be measured as a psychological/psychiatric construct but also as a state of chronic inflammation. Latent variables could be used to cluster individuals that have in common different levels of anxious-depression with different levels of common neuronal and peripheral inflammatory biomarkers. For instance, latent variable analyses could cluster different categories of anxious-depression with levels of IL-1 to evaluate the association of inflammation with anxious-depression. Latent variable models are becoming popular in behavioral medicine research because of their flexibility to measure different constructs (biological and psychological) and ease to be reproduced in other studies^{67–69}.

Conclusion

This manuscript proposes a hypothesis in which the dimensional construct of anxious-depression could serve as a direct measure chronic inflammation. Screening for negative emotional states such and anxiety and depression is considered essential in the initial work-up of patients with chronic inflammatory states such as metabolic syndrome and cardiovascular disease^{39,45,70,71}, therefore, is viable to consider that anxious-depression is an inflammatory phenomenon that is contributing to the exacerbation of chronic medical conditions. As described in the multinational large case-control INTERHART study, around 33% of causes of myocardial infarction are associated with psychological symptoms, being anxiety and depressive symptoms the most common ones^{70,72}.

The latent variable analytic approach will facilitate to study how clusters of anxious-depression are directly associated with inflammatory biomarkers. As several experts have cautioned in the past, it is important not to ignore the clustering of psychological factors that may act synergistically in the progression of a chronic illness^{73–75}.

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Figure 1. Theoretical Model of the Anxious-Depression as an Inflammatory State

Inflammation is characterized by HPA hyperactivity, immune dysregulation, increased monoamine activity, increased pro-inflammatory cytokines, cardiovascular reactivity and altered coagulation factors. The different symptoms of anxious-depression share the same biological processes observed in inflammation. This theoretical model supports the hypothesis that anxious-depression is an inflammatory state.