4-3-2018

Pro-inflammatory Cytokines and Depression

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Independent Study, N997

April 3rd, 2018

Abstract

Depression is the leading cause of disability worldwide and its prevalence continues to grow. Depression is one of the major risk factors for suicide, which is also on the rise. Even those who are treated for depression continue to suffer, as the current recommended treatment for depression rarely lead to remission or resolution. Recent research has focused on finding adjunctive treatments to conventional anti-depressant therapy; and has found that there may be a link between systemic inflammation and symptoms of depression. In this review, current literature studying the association of inflammation and depression was analyzed to answer the question, “Do pro-inflammatory cytokines play a role in the pathophysiology of depression?” Cross-sectional, longitudinal, and meta-analytical studies were systemically reviewed, and the collective data suggests that there is an association between inflammatory cytokines IL-6 and TNFα, as well as inflammatory marker CRP, and depression. Although more research is required prior to formulation of new guidelines for treating depression, this data suggests the possibility of effective adjunctive anti-inflammatory therapy for treatment of depression.

Pro-inflammatory Cytokines and Depression

Depression is a debilitating disorder that affects more than 300 million people globally. It is defined by symptoms of sadness, fatigue, anhedonia, feelings of guilt or low self-worth, disturbed sleep or appetite, and poor concentration that cause significant impairment in social, occupational, or other important areas of functioning (American Psychiatric Association, 2013). Depression is the leading cause of disability worldwide and the key precipitating factor for suicide. Between 2005 and 2015, people living with depression worldwide increased 18.4% (World Health Organization, 2017). According to the World Health Organization (WHO), this number is expected to continue to rise (2017). In the United States alone, it is estimated that 16 million people are suffering from a depressive disorder, amounting to about six percent of the population (Institution for Health Metrics and Evaluation, 2018). This devastating fact has made suicide the second leading cause of death in the United States for those ages 15-29 years old (WHO, 2017). Depression is a global burden in which the prevalence continues to increase (WHO, 2017). It demands the attention of global research, as well as government and healthcare leaders.

These statistics point to the fact that something more must be done to control this growing epidemic. A portion of those suffering from depression may not be receiving the recommended treatment or not receiving treatment at all. However, it is estimated that one-third of those who are being treated according to current pharmacological treatment guidelines remain unresponsive (WHO, 2017). Globally, this equates to approximately 100 million people who are still suffering from depressive symptoms even after receiving recommended pharmacotherapy. In addition, the two-thirds of those who do respond to conventional anti-depressant treatment often do only partially, never fully reaching recovery (Rush et al., 2006). These facts indicate

that the pathophysiology of depression and its complexity are still not completely understood; and they highlight the need for more research and adjunctive therapies for treating depression.

In search for a better understanding of depression and its treatments, current research has proposed that inflammation may play a role in the pathophysiology of some depressive disorders; causing a substantial cohort of those treated solely with anti-depressants unresponsive. Research has questioned if this cohort also correlates with the partial treatment response seen in many of those treated with conventional anti-depressants. There has been a flood of research looking at the association between inflammation, biological markers of inflammation, and depression. The main biological markers of depression under current research include cytokines, chemokines, and C-reactive protein. In this literature review the following question will be addressed: Do pro-inflammatory cytokines play a role in the pathophysiology of depression?

Purpose and Significance

The focus of this study is to better understand depression and the role that inflammation plays in its pathophysiology. It is the hope that with this understanding, adjunctive therapies for treating depression will be found. Currently, the primary accepted hypothesis for depression is the monoamine hypothesis. This hypothesis proposes that it is the depletion of monoamines in the brain, such as serotonin and norepinephrine, that cause depressive symptoms. From this hypothesis, it follows that most anti-depressant treatments revolve around increasing the availability of monoamines in the brain (Raedler, 2011). Current pharmacological treatment guidelines according to the American Psychiatric Association (2010) are based upon the monoamine hypothesis and include treatment with anti-depressants such as with a selective serotonin reuptake inhibitor (SSRI), selective norepinephrine reuptake inhibitor (SNRI), mirtazapine, or bupropion. However, it seems that this hypothesis is incomplete as treatment

outcomes are sub-par. When followed, these recommendations show limited efficacy in both research and clinical practice (Raedler, 2011).

The limited efficacy of this recommended antidepressant treatment was demonstrated in the highly regarded STAR*D Trial (Rush et al., 2006). The findings concluded that approximately one-third of those who receive treatment with an SSRI will obtain remission or become symptoms free. For those whom initial SSRI therapy fails, switching to or adding another APA recommended antidepressant, will likely only result in a 33% or 25% chance of remission, respectively. Research indicates that the higher the number of antidepressant medication trials, the greater the likelihood of treatment failure (Rush et al., 2006). It is prudent to point out that those who participated in this study were diagnosed with uncomplicated depression, and yet many did not obtain remission. It is well known that many individuals meeting criteria for a depressive disorder diagnosis also suffer from additional comorbid psychiatric conditions, leading to higher levels of treatment resistance. The STAR*D Trial highlights three key points: the pathophysiology of depression is complex, there is limited efficacy in treating depression with conventional antidepressants, and additional treatment options are needed for remission of depression to be a possibility.

This research supports the limited efficacy of current guidelines in treating depression solely according to the monoamine hypothesis. It calls for additional research, hypotheses, and understanding of the complex pathophysiology of depression so that adjunctive treatments and complete remission from depression can be made possible. By better understanding how pro-inflammatory cytokines contribute to the pathophysiology of depression, it is the hope that adjunctive treatments can be discovered, and the outcomes for those suffering with depression improved.

Theoretical Framework

To appreciate the role that proinflammatory cytokines have in depression, the Stress-Response Theory must first be understood. The concept of allostasis and allostatic load will also be discussed in the context of the Stress-Response Theory. These concepts together help relate how chronic stressors lead to excessive adaptive mechanisms which negatively alter the inflammatory cytokine response. This understanding will create the basis for relating stress, inflammation, and depression.

The Stress-Response Theory proposed by Hans Selye describes the relationship between stressors and physiological adaptations to stress. Selye described stress as "a state manifested by a specific syndrome of the body developed in response to any stimuli that made an intense systemic demand on it" and stressors as, "events or environmental agents responsible for initiating the stress response" (Grossman & Porth, 2014, p. 205). He believed that stressors are events that challenge homeostasis and that disease was the consequence of a failed adaptive system that could not keep the body in homeostasis (Rice, 2012). Selye proposed that stress was the common denominator to all adaptive physiologic changes and that these changes occurred both locally and systemically (Rice, 2012).

Selye termed the local physiological changes in response to stress as the general adaptation syndrome (GAS). This syndrome consists of three stages and is initiated when a stressor presents itself that exceeds the organism's current adaptive abilities and resources. The stages are as follows: the (1) alarm stage, which is the physiologic initiation of the sympathetic nervous system and the HPA axis, the (2) resistance stage, in which the body initiates the most reasonable response to the stress placed upon it, and the (3) exhaustion stage, which occurs if the

stressor continues to defy the body's defense system, leading to depletion of resources and systemic damage (Grossman & Porth, 2014).

Normally, the organism can adapt to the stressor and maintain homeostasis before getting to the exhaustion stage of the GAS. In this case, the stress response ends in the resistance stage and aids in survival. It is in this stage that various physiological systems make changes to maintain internal stability outside of the normal homeostatic range, also known as allostasis. When the stressor outweighs the organism's adaptive abilities and the allostatic load is too great, exhaustion occurs. It is in the exhaustion stage that the HPA axis, or neuroendocrine system, is overactive leading to excessive levels of circulating cortisol. The chronic excess of circulating cortisol and other hormones in the exhaustion stage have negative effects on many physiologic systems such as the circulatory, digestive, and immune systems and can accelerate disease processes (Grossman & Porth, 2014; Rice, 2012).

It is when focusing on the immune system and how it is affected by the hyperactive neuroendocrine response to stress, that cytokines come into play. In Selye's Stress-Response Theory, the endocrine-immune interaction is important because both physiologic systems share the same signaling pathway, including circulating molecules such as hormones and neuropeptides, that can influence the production of cytokines and other proinflammatory molecules. Immune cells, such as helper T cells and macrophages, are triggered by stress, penetrate the blood brain barrier, and release cytokines that in-turn exacerbate the stress response and negatively affect other neurological systems (Grossman & Porth, 2014). It is in this way that stress, Selye's exhaustion stage, and cytokines may play a role in the pathophysiology of depression.

The Stress Response Theory, the concept of allostasis, and the endocrine-immune process are the most relevant in framing the foundation to understand the relationship between cytokines and depression. In summary, stress can overwhelm an organism's adaptive abilities leading to exhaustion and an overactive HPA axis or neuroendocrine system. This overactivation leads to excess levels of circulating cortisol which can induce he inflammatory response (Grossman & Porth, 2014; Rice, 2012). Cytokines are released in this inflammatory response and are thought to induce depression by three separate mechanisms, which will be discussed in the following sections.

Definitions: Inflammation and Depression

The inflammatory hypothesis for depression has received much attention as of late, in the hope that inflammatory markers such as cytokines, may help in detecting and treating a subset of those suffering from depression. It has been suggested by multiple studies that inflammation induces a type of "sickness behavior" that has similar symptoms to that of depression. These symptoms include anhedonia, fatigue, loss of appetite, psychomotor slowing, cognitive impairments, and sleep disturbances (Krishnadas & Cavanagh, 2012; Liu, Adibfar, Herrmann, Gallagher, & Lanctot, 2016). It is hypothesized that inflammation and its cytokine processes may alter neurofunction leading to these depressive symptoms and depression.

Inflammatory cytokines are subdivided into two groups; the pro-inflammatory cytokines and the anti-inflammatory cytokines. The pro-inflammatory cytokines consist of interleukin-1 (IL-1), interleukin-1β (IL-1β), interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-12 (IL-12), interleukin-18 (IL-18), interferon gamma (INFγ), granulocyte-macrophage colony stimulating factor, and tumor necrosis factor alpha (TNF-α) (Liu et al., 2016). These cytokines are released and induce central nervous system (CNS) inflammation which is thought to lead to depression

through the three following mechanisms as shown in Figure 1: (1) alterations in the neuroendocrine system through hypothalamic-pituitary-adrenal (HPA) axis functioning, (2) changes in neurotransmission pathways, and (3) by impairing neurogenesis, neuroplasticity, and neuroprotection (Kiecolt-Glaser, Derry, & Fagundes, 2015; Kim, Na, Myint, & Leonard, 2015; Liu et al., 2016; Makhija & Karunakaran, 2012; Raedler, 2011).

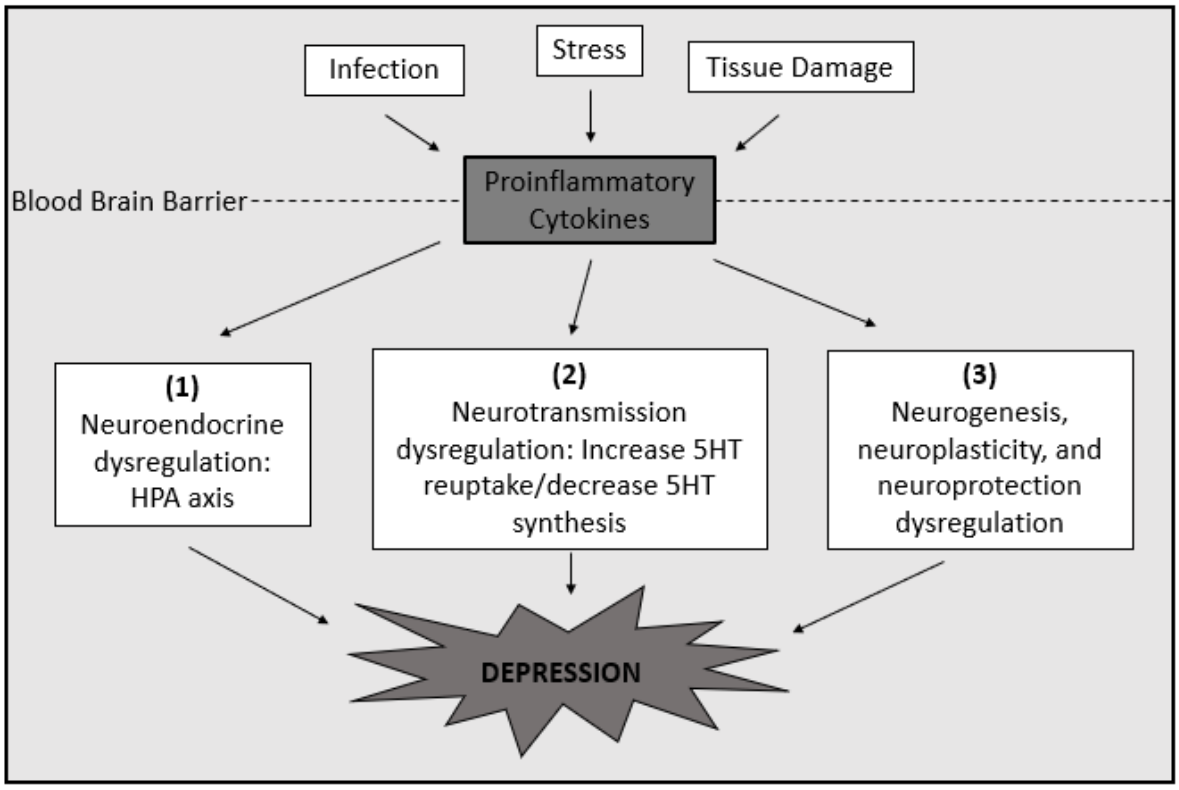

Figure 1. The three mechanisms by which proinflammatory cytokines induce depression. Adapted from Postal and Appenzeller (2014).

Neuroendocrine dysregulation: HPA axis

As mentioned previously regarding Selye's Stress Response Theory, excess stress can induce HPA axis functioning which in-turn induces the inflammatory response and release of cytokines. Interestingly, this release of cytokines can also further dysregulate HPA axis

functioning by causing glucocorticoid receptor resistance leading to overactivation of the HPA axis. This overactivity can have far reaching effects on the human body as it controls many downstream physiological mechanisms and can lead to abnormalities, such as steroid insensitivity and cortisol hypersecretion (Kim et al., 2015; Krishnadas & Cavanagh, 2012; Makhija & Karunakaran, 2013). These mechanisms, caused by increased proinflammatory cytokines and glucocorticoid resistance are thought to contribute to depressive symptoms by altering various neurochemical pathways and proper neurogenesis (Kim et al., 2015; Krishnadas & Cavanagh, 2012).

Neurotransmission dysregulation

Increased levels of proinflammatory cytokines also play a role in altering neurotransmission pathways contributing the pathogenesis of depression. Cytokines both decrease serotonin synthesis as well as increase its reuptake leading to depressive symptoms (Kiecolt-Glaser et al., 2015; Kim et al., 2015; Krishnadas & Cavanagh, 2012; Liu et al., 2016; Makhija & Karunakaran, 2012; Raedler, 2011). Serotonin levels are indirectly affected by an increase in tryptophan metabolism. Cytokines, especially IL-1β and TNFα, induce the kynurenine pathway which is responsible for metabolizing tryptophan into molecules other than serotonin. By inducing the kynurenine pathway and utilizing more tryptophan there is less tryptophan available for serotonin synthesis leading to decreased serotonin levels and neuronal signaling; therefore increasing depressive symptoms. In summary, cytokines induce a process that decreases the amount of available serotonin for neurotransmission, while also increasing levels of kynurenine and quinolinic acid; which are also thought to independently affect mood and induce depressive symptoms through various toxic measures (Kim et al., 2015; Krishnadas & Cavanagh, 2012; Makhija & Karunakaran, 2012; Postal & Appenzeller, 2015; Raedler, 2011).

An additional mechanism by which proinflammatory cytokines, especially TNF-α, affect serotonin transmission is through increased serotonin reuptake. Cytokines induce this effect by stimulating the MAPK pathway, which is responsible for increasing transport of serotonin, norepinephrine, and dopamine back into the neuron. Increased reuptake of these neurotransmitters into neurons results in low levels of neurotransmitters available in the synaptic cleft for signal transduction and normal neurotransmission. This resulting abnormality, as follows from the monoamine hypothesis, also induces depressive symptoms (Kim et al., 2015; Krishnadas & Cavanagh, 2012; Makhija & Karunakaran, 2012; Postal & Appenzeller, 2015; Raedler, 2011).

Dysregulation of neurogenesis, neuroplasticity, and neuroprotection

Lastly, proinflammatory cytokines induce depression by altering neurogenesis, neuroplasticity, and neuroprotection (Kiecold-Glaser et al., 2015; Kim et al., 2015; Krishnadas & Cavanagh, 2012; Liu et al., 2016; Makhija & Karunakaran, 2012; Postal & Appenzeller, 2015, Raedler, 2011). The most abundantly studied proinflammatory cytokines which have negative effects on these processes include IL-6, TNF-α, and IL-1β. These cytokines contribute to cellular oxidative stress which leads to damage in certain areas of the brain, such as the prefrontal cortex and amygdala, affecting mood (Kiecolt-Glaser et al., 2015). In addition, several studies have shown that abnormal levels of these cytokines inhibit neuronal growth, especially in the hippocampal regions of the brain affecting vital cognitive functions (Kim et al., 2016). These cytokines can also negatively affect the production of neuroprotective factors, such as brain-derived neurotrophic factor (BDNF) in vital areas of the brain through glutamate dysregulation and excitotoxicity (Kiecolt-Glaser et al., 2015). It is through these mechanisms of dysregulation that inflammation plays a role in the pathogenesis of depression.

Process

To gain a better understanding of the pathophysiology of depression and what role pro-inflammatory cytokines play in it, an online literature search was completed. The following academic databases were searched in December of 2017: CINAHL, PubMed, PsychologyOnline, PsychINFO, ScienceDirect, and SCOPUS. The key terms used in different combinations included the following, “Inflammatory”, “anti-inflammatory”, “immune”, “immune response”, “cytokines”, “depression”, “major depressive disorder”, “major depression”, “inflammation-associated depression”, and “C-reactive protein.”

Initially the articles selected were reviewed based upon dates, titles, and abstracts. Articles were only included if they were published between 2008-2018, with a focus on more recently published articles. Studies were assessed and excluded if they: (1) had subjects under the age of 18; (2) were an animal-based study; (3) included subjects with comorbid medical diseases, such as cancer, cardiovascular, or pulmonary diseases. There is a plethora of literature that assess the association of inflammation in chronic disorders and the role this inflammation plays in depression. However, the interest of this review is that solely of depression and inflammatory markers associated with this disease state, so articles that did not also have this focus were eliminated as well. After gathering the remaining articles, each reference list was searched based on title and date so that any articles missed were collected. With this search a substantial number of relevant articles were added for analysis.

The focus of this literature review was to answer the clinical question, “Do pro-inflammatory cytokines play a role in depression.” In the search for an answer, it was found that much of the literature focused on three pro-inflammatory markers, CRP, IL-6, and TNFα. Throughout the search, some of the literature looked at various other cytokines but the

association between them and depression was rarely found to be significant. Therefore, the review was limited to those studies that compared the association between IL-6, TNFα, CRP and depression. IL-6 and TNFα are considered pro-inflammatory cytokines, however CRP is not. Rather, CRP is an acute-phase protein that's synthesis is induced by pro-inflammatory cytokines IL-1β, IL-6, and TNFα (Sheldon, Riches, Gooding, Soni, & Hobbs, 1993). CRP is relevant when focusing on cytokines because the level of CRP is thought to be directly related to levels of circulating pro-inflammatory cytokines; therefore, it was included in the literature review. This review is primarily focused on more recent studies, carried out within the last 5 The final collection of literature included 30 articles which were organized based upon content, level of evidence, and date. Approximately 15 articles were review articles that were used for collateral information throughout this research paper, while the 15 remaining articles were critically analyzed.

The critical analysis of these articles was completed; (1) so that the abundance of data available regarding inflammatory cytokines and their role in depression could be compiled and compared; (2) to see which specific inflammatory markers play the greatest role in depression; and (3) to be one step closer to better understanding and treating depression. The target audience is that of nursing and psychiatric research, especially for those in research based psychiatric advanced practice nursing roles. It is hoped that with dissemination of this project nursing leaders and researchers will be reminded that the etiology of depression is still not completely understood, and that there is noteworthy evidence that inflammation plays a role in depression. It is anticipated that with this greater understanding that interest will be sparked in finding new adjunctive treatment options for depression.

Literature Review

Cross-sectional Studies

Many studies have aimed to find an association between inflammation and depression, but few have looked at the bidirectionality of the relationship. A study by Gimeno et al. (2008), looked at this relationship and sought to assess whether inflammatory markers such as IL-6 and CRP predict depression, or if depression predicts these inflammatory markers. This study was embedded in the Whitehall study, which was an ongoing large-scale occupational cohort study including 6895 men and 3413-woman subjects age 35-55 years. The study by Gimeno et al. (2008), assessed a final cohort of 3353 subjects who had CRP data available and 3070 who had IL-6 data, both which also had been assessed for depression symptoms at baseline. Depressive symptoms were measured with a portion of the General Health Questionnaire (GHQ), which is used to assess psychiatric disorders. Twenty-eight items from the GHQ which assessed cognitive symptoms of depression only.

A strength of this study was the that they included important correlates of inflammation and depression as covariates. The covariates included sociodemographic data, health-related behaviors such as alcohol consumption, diet, exercise, body mass index (BMI), and inflammatory medical conditions such as coronary heart disease. Strict statistical analysis was also used to assess directionality between the variables of inflammatory markers and depression. The major limitation of this study is how depression was assessed, as not all required symptoms for the diagnosis of depression were measured.

The study found that over a 12-year period, inflammatory markers IL-6 and CRP at baseline were associated with increased levels of cognitive symptoms of depression at follow up.

They found that this association remained even after controlling for the covariates. It was also found that increased depression at baseline did not predict increased levels of IL-6 or CRP at follow up. In conclusion, the results suggest a moderate level of evidence that the association between inflammatory markers and depression is unidirectional from inflammatory markers to depressive symptoms.

In another cross-sectional cohort study by Wium-Anderson et al. (2013), they tested whether elevated CRP levels were associated with symptoms of psychological distress and depression. To test this, the study measured CRP levels in 73,131 subjects from the Copenhagen General Population Study and the Copenhagen City Heart Study. This population included those of Danish decent, who were 20 years or older. CRP was measured in all the subjects, as was psychological distress and depression. Depression was assessed based upon 3 methods: (1) self-report of antidepressant use, (2) history of antidepressant use for 6 months based upon the Danish Register of Medicinal Product Statistics, and (3) a depression diagnosis upon hospital discharge based upon the ICD-8 and ICD-10. Prior to determining results, the data was adjusted to control for age, sex, alcohol intake, smoking, physical activity, annual income, education level, BMI, and register-based chronic disease.

Using cross-sectional analysis, it was found that higher CRP levels were positively associated with both self-report and prescription registered anti-depressant use. This analysis also indicated that higher levels of CRP increased one's risk for future hospitalization with depression. In a prospective analysis conducted by Wium-Anderson et al. (2013), it was found that those who had a history of being hospitalized more often, were associated with increased levels of CRP. The strength of these findings included the large cohort of subjects analyzed, as well as the availability of data regarding subjects taking antidepressants and their doses. This is a

limitation as well, as the measured CRP levels may have been altered by the antidepressants, as several studies have shown that treatment with anti-depressants results in decreased levels of inflammatory markers (Dahl et al, 2014; Schmidt et al, 2016). Also, it is important to note that anti-depressants are many times prescribed for diagnoses other than depression and this study assumed that if a patient was taking an antidepressant, they were taking it for depression. Another significant limitation of this study is that the design did not allow for assessment of depression and measurement of CRP levels at similar points in time. Depression was assessed based upon use of anti-depressants and hospital admissions, which doesn't necessarily mean that the subject was experiencing depressive symptoms at the time of CRP measurement.

In conclusion, this study shows limited evidence that increased CRP levels are associated with depression. The unreliability of the diagnosis of depression and depressive symptoms, along with the fact that many subjects were taking antidepressants. The multiple and varying limitations suggest that the results should be considered carefully.

To assess a population free from chronic medical disorders that may have influence over chronic inflammation and inflammatory markers, Liu et al. (2014), assessed a population strictly controlling for confounding variables as such. The study compared the relationship of CRP and depression in a cohort of 6396 men and 6610 women free of chronic medical illness. The participants were 18 or older and data was gathered from NHANES survey conducted by the CDC from 2005-2010. Depressed mood was assessed with the PHQ-9 and the diagnostic criteria from the DSM-IV. Only those subjects whose data were available on family income, education, BMI, and history of major medical illnesses were included.

Strengths of this study include the fact that a wide variety of covariates were considered, and results were analyzed after controlling for many of these. Also, the diagnosis of depression

was standardized and reliably measured. While limitations include the cross-sectional design of the study, the main limitation included the incomplete information on whether subjects were taking psychotropic or anti-inflammatory medications, similar to the study by Wium-Anderson et al. (2013). It is important to note that not controlling for those subjects taking anti-inflammatory or antidepressant medication could have severely altered the results.

The results indicated a significant association between CRP and depression in men, but only in women after correcting for body weight. This finding may indicate that BMI may play a greater role in depression than prior studies suggest (Liu et al., 2014). The study also carried out a thorough statistical analysis suggesting that chronic medical illnesses, or a history of, have limited impact on the relationship of CRP and depression; meaning that systemic inflammation and depression may be independent from medical illnesses (Liu et al., 2014). This study brings to light important areas for consideration, however due to its failure to control for certain variables, it only provides limited evidence that inflammatory markers, such as CRP, play a role in the pathophysiology of depression.

In more recent study by Kohler-Forsberg et al. (2017), the relationship between CRP levels and overall depression symptoms severity was investigated. This study analyzed data from the Gnome-Based Therapeutics Drugs for Depression study, an open-label randomized clinical trial. Two-hundred and thirty-one individuals with a diagnosis of MDD of at least moderate severity were assessed for CRP levels that were less than 10mg/L, being that greater levels indicate acute inflammation rather than chronic (Kohler-Forsberg et al., 2017). At baseline, subjects were assessed for depression with the Montgomery-Asberg Depression Rating Scale (MADRS) and the 17-item Hamilton Depression Rating Scale, and the Beck Depression Inventory; each performed by a psychologist or psychiatrist. Serum CRP was collected and

assessed at baseline as well. It is important to note that the subjects included in this study were taking either nortriptyline or escitalopram antidepressant.

The study found a significant association between CRP levels and depression severity. Kohler-Forsberg et al. (2017) found that those with a CRP <1mg/L (N=131) had a mean MADRS score of 29.6 indicating moderate depression, and those with a CRP from 7-10mg/L (N=7) had a mean MADRS score of 35 indicating severe depression. This finding was only significant for women. Interestingly, it was found that subjects with higher levels of CRP were those of older age, higher BMI, smokers, and less educated than those with lower levels of CRP. When looking at symptom type, it was found that the severity of observed mood, interest in activity, cognitive symptoms, neurovegetative symptoms, and suicidality increased, which was especially apparent in women (Kohler-Forsberg et al., 2017).

The strengths of this study included the large sample size, the thorough assessment of depressive symptoms and depression diagnoses, and ability to adjust for multiple covariates. This study included subjects that were taking antidepressants, like the studies by Wium-Anderson et al. (2013) and Liu et al. (2014). However, every subject in the current study was taking one of two antidepressants, compared to the other studies where it was unclear whether or not subjects were taking medication, which was not controlled for. Therefore, the main limitation is the cross-sectional design of the study, further study should include longitudinal analysis of depression, treatment, and CRP levels.

In another recent cross-sectional study by Tayefi, et al. (2017), a gender-stratified examination of the association between high sensitivity-CRP (hsCRP) and depression/anxiety was completed. The aim of the study was to assess if CRP is positively associated with depression/anxiety and if gender plays a role in this relationship. The cohort analyzed included

9759 subjects from northeastern Iran using a stratified cluster method from the MASHAD study. The MASHAD study was a cohort study looking at biopsychosocial risk factors for cardiovascular disease in urban dwelling 35-65-yearolds. The subjects included in the current study by Tayefi, et al. (2017), excluded those taking antidepressant medication, unlike the previous studies discussed. To measure level of depression in this sample, the Beck Depression Inventory (BDI) was used. The results were assigned to 4 categories based upon no, mild, moderate, or severe depression.

The results indicated a significant positive association between the level of CRP and severity of depression/anxiety, especially for depression in men. These results follow that an enhanced inflammatory state, as indicated by increased CRP levels, is associated with depression severity. Interestingly the study found that depression scores increased with BMI for women and increased for both sexes regarding smoking. Both BMI and smoking were found to be the strongest determinants for depression/anxiety. Both increased BMI and smoking have been shown to affect the inflammatory state of the body, increasing risk for depression (Tayefi et al., 2017).

The results of this study show strong evidence that the inflammatory marker CRP is associated with a depressive state. The strengths of this study aide in this evidence and are as follows: large sample size, population-based study, standardized assessment for depression, and absence of medication that may alter results. The limitations, however small, included the design of the study limiting the association to bidirectional, rather than finding a directional association. In conclusion, this study adds to the evidence supporting inflammation associated depression.

In a population-based cohort study, van Dooren et al. (2016) aimed to evaluate the independent associations of inflammation and endothelial dysfunction with depression. The

review of this literature will focus on the association found between inflammatory markers, IL-6, hsCRP, and TNFα. The data for this study was gathered from the previous Maastricht Study, an observational prospective population-based cohort study (van Dooren, et al., 2016). The present study included 852 subjects, between the ages of 40 and 75 from the Netherlands diagnosed with depression. Depression was assessed with a Dutch version of the PHQ-9 and the Mini-International Neuropsychiatric Interview based upon the diagnostic criteria of the DSM-IV. Further characteristics of the sample were assessed and controlled for; characteristics such as partner status, diabetes, smoking behavior, alcohol consumption, physical activity, and history of cardiovascular disease. Depression and serum biomarkers were assessed at baseline.

The resulting data showed an association between CRP and TNFα with depression. The relationship was significant for CRP, following suit from previous data. TNFα also was found to be significant. IL-6 was not found to be associated with either depressive symptoms or depressive disorder. When collectively looking at all inflammatory biomarkers assessed, which included CRP, Serum amyloid A, soluble intercellular adhesion molecule-1, IL-6, IL-8, and TNFα, a significant association was found between inflammatory markers and depression.

The strength of this study included its sample size, assessment of depression with both a self-report and diagnostic interview, and that possible cofounding variables were assessed and controlled for. It is also important to note that there was a loss of power in statistical analysis due to missing values for depression and CRP levels in some subjects, which may have been a limiting factor. This study was of cross-sectional design, so it cannot draw conclusions as to the direction of the association between inflammatory markers and depression. Overall, this study provides moderate evidence that inflammatory markers, especially CRP and TNFα, are

associated with depression independent of age, sex, diabetes, glomerular filtration rate, cardiovascular disease, and lifestyle factors such as smoking, alcohol consumption, and BMI.

Interesting results were found by Zalli, et al. (2014) in a population-based cohort study which was embedded in the Rotterdam Study. The Rotterdam Study included inhabitants age 55 or older living in a defined geographical area of Rotterdam, Holland. The participants included 233 men and 423 women older than 60 years who were free of anti-depressant therapy. Serum biomarkers, IL-6, CRP, and alpha-1-antichymotrypsin were assessed at baseline. Depression was assessed based upon the Center for Epidemiologic Studies Depression Scale (CES-D) both at baseline and after 5 years.

The finding at baseline was that there was no association between depression and inflammatory markers at baseline. However, it is important to note a significant limitation that 102 of the participants were currently taking anti-inflammatory medications. This fact likely altered serum inflammatory markers, possibly leading to the insignificant resulting association of depression and inflammatory markers at baseline. Additionally, this finding may suggest that acute inflammation is not associated with depression, but only with chronic inflammation, in which this study did not assess. This study did find, however, that higher baseline levels of IL-6 and CRP were associated with significantly increased levels of depression after 5 years. But, when adjusting for physical illness this association was lost. This fact may indicate inflammatory markers only affect a subgroup of those suffering from depression, those with treatment resistant depression (Zalli, et al., 2014).

The strength of this study was its length, being that of 5 years. Its limitations included not controlling for anti-inflammatory medications, limited exclusion criteria, age of participants, and that it did not repeat serum marker levels after 5 years so that the analysis of whether or not long-

term exposure to inflammatory markers is associated with depression could not be assessed. In conclusion, this study provides limited support relating inflammatory marker IL-6 and CRP to depression. This study is important however, because it suggests that these inflammatory markers may predict the onset of depression; indicating that it is the chronic elevation of inflammatory markers that may increase one's risk for depression.

Longitudinal Studies

A longitudinal study by Dahl et al. (2014) investigated the relationship between cytokines and depression at baseline and after 12 weeks of antidepressant therapy. The study included 50 unmedicated subjects diagnosed with MDD and 34 healthy controls. Depression was assessed as a score 22 or greater on the Inventory of Depressive Symptomatology (IDS) scale. Depression level and blood samples were collected upon initiation of the study and compared. The blood sample was collected to assess the following: IL-1β, IL-1Ra, IL-2, IL-5, IL-6, IL-7, IL-8, IL-10, IL-15, granulocyte colony-stimulating factor, macrophage inflammatory protein 1 alpha, TNFα, and interferon gamma.

Dahl et al. discovered that 9 of the 13 cytokines were significantly increased in subjects with MDD compared to the controls, including IL-6; however, no significant differences were found for TNF-α comparing subjects to controls. Forty-three of the 50 subjects with MDD completed a 12-week trial of "treatment as usual" which included whatever therapy a single physician deemed best. The treatments included both antidepressant therapy and talk therapy. For this cohort of subjects completing therapy 7 of the 9 cytokines that were initially elevated, decreased significantly with response to treatment, including IL-6. It is important to note that with treatment levels of cytokines decreased along with depressive symptoms; at this time no significant difference was found in cytokine levels of those with MDD versus healthy controls.

Strengths of this study include the broad assessment of inflammatory markers, an adequate length of a 12-week study, and consistency with evaluators/physicians. Some important limitations to consider would be the small sample size, and the fact that subjects included in the study were being referred to a specialized psychiatric clinic limiting the applicability of the findings. The main finding of the study was that certain cytokines are elevated in those with depression and that these cytokines return to normal levels when depressive symptoms subside. The overall conclusions from this study show a strong indication that IL-6 plays a role in depression, but not TNFα.

Similar to the study by Dahl et al. (2014), a longitudinal case control study by Schmidt et al (2016) explored the relationship between serum cytokine levels, symptoms of depression, and antidepressant treatment. The cytokines investigated included both pro and anti-inflammatory, as well as C-reactive protein. The study included 30 patients diagnosed with MDD according to the DSM-IV and 30 age-and sex-matched controls. The subjects were assessed for depression at baseline, prior to any antidepressant treatment, with the Hamilton Depression Rating Scale and the Beck Depression Inventory. Serum cytokine levels were also assessed at this time, including TNF-α, CRP, IL-2, IL-4, IL-5, IL-10, IL12, IL-13. Both depression and serum cytokine levels were assessed again after 4 weeks of antidepressant treatment, with either escitalopram or mirtazapine, or both.

The results indicated that all cytokines, both pro and anti-inflammatory, were significantly negatively correlated with depression severity. After the 4 weeks of treatment, cytokines were significantly reduced independent from the depression outcome. Strengths include use of a standardized interview form to rate depression and a single rater blind to time point of interview and cytokine levels. Another strength of this study was that it included a broad

range of cytokines, compared to most of the other studies on this subject. However, the results may be limited due to the short trial of antidepressants and time in between blood sampling. Another limitation may be that the sample of subjects was small, leading to the higher likelihood of type II errors.

The results indicated that both pro and anti-inflammatory cytokines are inversely correlated with severity of depression. Both pro and anti-inflammatory cytokines were significantly higher in treatment responders compared to non-responders. In conclusion, this study provides limited evidence that cytokines induce depression, rather it provides that cytokines may relate more to the severity of depressive symptoms, or not at all.

In another longitudinal case control study by Lidqvist et al. (2016) the association between inflammatory markers, oxidative stress, and depression were assessed. The study sampled inflammatory markers and markers of oxidative stress in 50 unmedicated subjects with MDD versus 55 healthy controls. The Hamilton Depression Rating Scale was used to assess depression in the MDD subjects. The blood samples were collected at the start of the study and included the following markers: IL-6, TNF-α, C-reactive protein, F2-isoprostanes, 8OH 2-dexoyguanosine, glutathione peroxidase, glutathione, and vitamin C. Following this initial sampling, 22 of the 50 MDD subjects began a trial of SSRI antidepressant therapy. After an 8-week period both depression rating and blood samples were collected again.

They found after correcting for age, sex, BMI, and smoking that inflammatory markers of IL-6 and TNF-α were significantly higher in the subjects diagnosed with MDD versus the healthy controls. In those treated with antidepressants for 8 weeks, there was a significant decrease in the level of inflammatory marker IL-6. The strength of these results is based upon the strict exclusion criteria carried out by the authors, and the variety of covariates they assessed.

The main weakness to note was that of the small sample size and the even smaller sample of those who received antidepressant therapy for analysis.

In conclusion, this study provides moderate support that inflammatory cytokines, such as IL-6 and TNFα, play a role in depression based upon the fact that those with MDD had higher baseline cytokine levels compared to healthy controls. This study also showed that responders to antidepressant therapy also saw a decrease in pro-inflammatory cytokines, further supporting inflammation associated depression.

Meta-analyses

In a meta-analysis by Howren, Lamkin, & Suls (2009), an association of depression with CRP, IL-1, and IL-6 was sought. The objective was to examine the magnitude and direction of these associations in community and clinical samples. A systematic review was completed and articles published between 1967 and 2008 were collected from PubMed and PsycINFO. The data was collected, and effect sizes were calculated and analyzed using the random-effects model (Howren et al., 2009). The overall results indicated that CRP, IL-6, and IL-1 were positively associated with depression.

When comparing association between CRP and depression there was found to be evidence of publication bias as well as significant heterogeneity. Therefore, several subgroup analyses were completed (Howren et al., 2009). The data showed that with increasing age, both inflammation and depression increased significantly. When controlling for BMI, there was only small association found, however in the studies that this was not controlled for the effect size was almost three times as large, indicating that BMI significantly influences the association between CRP and depression. The results of subgroup analysis of medication were inconclusive.

When looking at IL-6 a significant association was found as well, and again there was also an indication of publication bias and heterogeneity. With subgroup analysis, meta-regression found that increasing age was not related to increasing levels of IL-6, opposite as to what was found for CRP. Controlling for BMI, decreased the association between IL-6 and depression, again showing the influence that BMI has on this relationship. In the studies analyzed that controlled and adjusted for medication use, such as with antidepressants, had a greater effect size compared to the studies that did not control for this variable.

The results indicated a moderately sized positive association between IL-1 and depression (Howren et al., 2009). Opposite of the other analyses, little publication bias was found, however there still was significant heterogeneity and again subgroup analyses were conducted. When adjusting for BMI, the effect size was not significant, again indicating the influence of BMI on the association. When adjusting for medication use, the effect size was not significant compared to the minimal significance found when not adjusted for.

In review, CRP, IL-6, and IL-1 were found to be significantly associated with depression in both clinical and community samples. It is important to note that BMI when controlled for, significantly decreased the association between inflammatory markers and depression, however it did remain significant. The results are limited in that the direction of the relationship cannot be determined from this data. The causal relationship remains inconclusive. Another limitation was that studies were not excluded based upon other comorbid diseases such as cardiovascular disease that may have affected chronic inflammatory status. Also, there was significant heterogeneity noted throughout. Strengths included that subgroup analysis was conducted to help with some of the heterogeneity found, as well as the breadth of literature reviewed. In

conclusion, this meta-analysis provides moderate support for an association between CRP, IL-6, and IL-1 with depression.

Dowlati et al. (2010), conducted another meta-analysis on articles comparing cytokine levels in subjects diagnosed with depression to healthy controls. Studies were included: (1) if they used DSM-III or DSM-IV criteria for depression, (2) if they included subjects free of other comorbid diseases such as, cancer, pulmonary, or cardiovascular disease, (3) if the subjects were not using antidepressants, (4) if controls were psychiatrically healthy, and (5) if cytokine levels were measured in the morning prior to being stimulated. These inclusion criteria are one of the major strengths of this study. A literature search was conducted of MEDLINE, EMBASE, PsychINFO, Cochrane, Database of Systematic Reviews, AMED, and CINAHL from June 1960 to August 2009 (Dowlati et al., 2010). The search included the following pro-inflammatory cytokines: TNFα, IL-1β, IL-6, IL-2, IL-8, and IFNγ, and the anti-inflammatory cytokines IL-10 and IL-4. A total of 24 studies were collected. Significant heterogeneity was found so the random effects model was used for analysis.

The results indicated that there was a positive association found for both TNFα and IL-6. Data from 13 studies was extracted to assess TNFα. Measurements were made from 438 subjects with depression compared to 350 health controls. They found significantly higher concentrations of TNFα in the subjects with depression compared to the controls, with an overall weighted mean difference of 3.97pg/mL. For IL-6, there were 16 studies used to compare 492 subjects diagnosed with depression to 400 healthy controls. Patients with depression had significantly higher levels of IL-6 compared to controls with a weighted mean difference of 1.78pg/mL. The remaining cytokines assessed did not show significant association between levels in depressed subjects compared to controls.

As mentioned previously a major strength of this analysis was that of its exclusion and inclusion criteria. It is important to note that the studies analyzed had a control for comparison, as many current meta-analyses did not include this requirement. This meta-analysis excluded those studies with cofounding variables that may have affected the results, such as those with subjects taking antidepressants, and those with subjects with inflammatory diseases. The limitations of this study were minimal; however, it is important to note there was significant heterogeneity found and not all was controlled for. Overall, this meta-analysis shows strong evidence that TNFα and IL-6 are associated with depression.

In a more recent meta-analysis, Liu, Ho, and Mak (2012), also found that TNFα and IL-6 were significantly elevated in subjects diagnosed with depression compared to controls. It was also found that pro-inflammatory soluble cytokine receptor sIL-2R was significantly associated with depression. Liu et al. (2012), searched PubMed and EmBase for literature between 1960 and February 2011. The literature included cross-sectional study designs, and exclusion criteria were as follows: (1) subjects taking antidepressant or anti-inflammatory medication, (2) subjects with other comorbid medical or psychiatric disorders, (3) studies that did not involve a control group, and (4) studies that did not assess depression based on DSM criteria. After applied, a final 29 articles were collected for the meta-analysis and the following biomarkers were assessed: sIL-2R, TNFα, IL-6, IL-1β, IFNγ, IL-2, IL-4, IL-8, IL-10.

The results indicated a significant association between the proinflammatory cytokines IL-6 and TNFα, and the receptor sIL-2R. The analysis of IL-6 was assessed in 18 studies, and they found that patients with MDD had significantly higher levels of IL-6 than the control group. The mean difference between groups was 0.680pg/mL based upon the random-effects model due to the high level of heterogeneity. The analysis of TNFα was assessed in 15 studies, also finding a

significant difference between subjects and controls. The mean difference between groups was that of 0.525pg/mL also based off the random effects model. They determined after a meta-regression that the main source of heterogeneity was due to age. There was no significant difference between biomarkers in subjects with MDD compared to controls in the remaining anti-inflammatory and cell-mediated cytokines assessed.

The results of this meta-analysis are consistent with that of Dowlati et al. (2010), showing increased levels of both TNFα and IL-6 in subjects with MDD compared to controls. The current meta-analysis included 3 additional studies for IL-6 and 2 additional for TNFα. It is important to note that the current analysis by Liu et al. (2012) did not exclude subjects with comorbid depression and substance use, as did the analysis by Dowlati et al (2010). This would be considered a moderate limitation. Overall, even with this limitation the meta-analysis provides strong evidence for the association of IL-6 and TNFα with depression, due to its strict exclusion criteria and methodology.

In comparison to the meta-analyses by Dowlati et al. (2010) and Liu et al. (2012) which analyzed cross-sectional studies, a meta-analysis by Valkanova, Ebmeier, and Allan (2013), analyzed longitudinal studies to determine if inflammatory markers CRP and IL-6 increases the risk of subsequent depression. Literature was collected from Embase, Medline, and PsychINFO from 1970 to August 2012 and included longitudinal studies that included inflammatory markers at baseline and depression assessment at follow-up. A total of 9 articles were analyzed with an average follow up after 5 years. The aim of this meta-analysis is different than others in that it sought to determine the directionality of the relationship between inflammatory markers and depression.

From 8 studies, with 14,832 subjects, the results indicated a small but significant association between CRP levels at baseline and increased depressive symptoms at follow up. These results indicated moderate heterogeneity between studies and significant publication bias (Valkanova et al., 2013). Data for IL-6 was taken from 3 studies including 3695 subjects, and a slightly significant association was between baseline IL-6 and depressive symptoms at follow up. This association became non-significant after confounding variables were adjusted for. This may suggest that CRP at baseline is a better indicator for depression than IL-6 (Valkanova et al., 2013) However, the limited number of studies included in the IL-6 analysis may have contributed to this non-significant result.

The strengths of this analysis include the strict exclusion criteria and factors adjusted for, however the limitation is that of a small number of studies analyzed (n=9). The results show conservative support that inflammatory markers such as CRP and IL-6 precede depression. This does not mean however that these inflammatory markers are causal factors for depression. Rather that more research is needed to determine whether these markers are associative, mediating risk factors, or causal factors for depression (Valkanova et al., 2013).

A cumulative meta-analysis was conducted by Haapakoski et al. (2015), to examine the strength of association between inflammatory markers IL-6, IL-1β, CRP, and TNFα, and major depressive disorder. Literature published up until May 2014 was collected from PubMed, Embase, and PsychINFO. Inclusion criteria were (1) measurement of unstimulated cytokines; (2) comparison of adult subjects with MDD and psychiatrically healthy controls; (3) diagnoses of unipolar depression based on DSM-III or DSM-IV; and (4) subjects free of any major physical illness. The analysis did not exclude those taking medication but did acknowledge and label data as so. There were 58 articles included in this cumulative meta-analysis; 20 for CRP, 31 for IL-6,

31 for TNFα, and 14 for IL-1β. The results indicated that IL-6, CRP and TNFα were significantly associated with MDD. No association was found for IL-1β.

The cumulative meta-analysis for IL-6 showed a medium-sized association with depression. The data became statistically significant in 2006 and remained significant, even after the addition of 23 studies published between 2006 and 2014. For CRP, there was also a medium-size association with depression that became statistically significant after 14 studies and remained significant with the remainder of the published articles. For both IL-6 and CRP moderate heterogeneity was found but no publication bias. Lastly, increased levels of TNFα were found to be associated with MDD. Statistical significance was reached in 2009 after 14 studies were published and remained significant with the addition of 17 more articles. The heterogeneity was found to be high, with no publication bias. Haapakoski et al. (2015), carried out a sensitivity analysis and they found that the association between IL-6 and CRP with MDD remained significant even after excluding low-quality studies. This significant association was lost for TNFα. Interestingly, when adjusting for antidepressant use in the IL-6 and CRP studies, the significance remained and effect size increased.

The strength of this study is strong and supports the association between IL-6, CRP and depression, and minimal for TNFα with depression. The results regarding IL-6 and CRP confirm the results found previously in the meta-analyses by Dowleti et al. (2010), Liu et al. (2012), and Valkanova et al. (2013). There was a minimal association found between TNFα and depression, even though this inflammatory marker had the largest volume of published studies. These results may be due to a failure to control for appropriate confounding variables, or difficulties measuring this inflammatory marker (Haapakoski et al., 2015). Overall, this study shows strong

support for IL-6 and CRP being associated with depression, however it remains that more research is needed regarding the association between TNFα and depression.

Summary of Literature

The literature reviewed consisted of cross-sectional and longitudinal studies, as well as a handful of meta-analyses. Much of the original literature consisted of reviews, however this type of literature was not included in the analysis, rather it was used in providing background information. There were two studies that found no association between pro-inflammatory markers and depression; one for IL-6 and one for TNFα. However, the remainder of the studies found a positive association between these inflammatory markers and depression (Table 1). The greatest support was found for the association between IL-6 and depression, in 8 studies including several meta-analyses (Table 1).

The associations were deemed to be strong if the study, (1) had an adequate sample size, (2) controlled for possible covariates that may have influenced the inflammatory state, such as BMI, smoking, and inflammatory diseases, and (3) demonstrated significant association with strict statistical analysis. The remaining literature found limited to moderate associations between inflammatory markers and depression (Table 1). These limitations were due to the following factors: (1) inadequate control for external variables, such as antidepressant use,

	No Association	Limited Association	Moderate Association	Strong Association
CRP		3 studies	1 study	5 studies
IL-6	1 study	1 study		8 studies
TNFα	1 study			4 studies

Table 1. Literature analyzed and strength of association between pro-inflammatory markers CRP, IL-6, and TNFα and depression.

(2) inadequate assessment of depression and depressive symptoms, and (3) cross-sectional study design, limiting the findings to unidirectional associations.

Also, the data supported that CRP, IL-6, and TNFα levels were increased in those with depression at baseline, and when the depression subsided so did the level of the biomarkers. Overall, the literature indicates that pro-inflammatory markers CRP, IL-6, and TNFα play a role in depression and the severity of depressive symptoms, however, there is limited data available regarding the directionality of this relationship. It remains unclear whether inflammation precedes depression, or vis versa.

Interpretation/Outcome

The clinical question, "Do pro-inflammatory cytokines play a role in depression," was answered through this literature review. Collectively, the literature supports that there is a positive association between two of the pro-inflammatory cytokines and depression, IL-6 and TNFα. In accordance with the Stress Response Theory, it seems that stress is a precipitating factor for depression leading to immune dysfunction. This immune dysfunction includes the release of excess cytokines, leading to depressive symptoms by way of (1) HPA dysfunction, (2) neurotransmission dysregulation, and (3) altered neurogenesis. Being that only IL-6 and TNFα were found to be significantly associated with depression, with other pro-inflammatory cytokines being associated, however insignificantly; it seems that it may be the joint collection of pro-inflammatory cytokines that have the greatest effect on inducing depressive symptoms. It is possible that it is the collective balance between pro- and anti-inflammatory cytokines that aide in the pathophysiology of depression, however more research is needed to support this theory.

There is also evidence that suggests those who do not respond to conventional anti-depressant therapy may have elevated inflammatory profiles; suggesting there may be a subtype of depression that may benefit from alternate treatment, such as anti-inflammatory treatment regimens. The results from a meta-analysis of randomized clinical trials by Ole Kohler et al (2014), suggest that add on therapy with NSAIDS to conventional anti-depressant treatment increased subject response. Most notably, it was found that the NSAID celecoxib decreased depressive symptoms without an increase in adverse effects. There is also research that suggest other anti-inflammatory therapies such as treatment with vitamin D, omega-3-fatty acids, aspirin, curcumin, minocycline, and cognitive behavioral therapy, may decrease depressive symptoms in addition to conventional psychopharmacological therapies.

While this literature review supports the association between inflammation and depression, there is also evidence against this association. There is much evidence in rodent models supporting that inflammation is not associated with neuroimmune activation (Liu et al, 2016). Also, a wealth of data shows that not all depressed subjects have elevated inflammatory profiles (Marques-Deak et al, 2007; Steptoe, Kunz-Ebrecht, & Owen, 2003; Stubner et al, 1999). It is possible that inflammation varies in different subtypes of depression, which this review did not consider being that it focused solely on subjects with typical major depression. For example, there is data supporting that subjects with atypical depression had higher serum levels of CRP, IL-6, and TNFα, than those with melancholic depression (Liu et al, 2016). Further research is needed to compare inflammatory profiles of subjects with varying types of depression.

Overall the current review, along with a substantial amount of other supporting data, suggests an association between inflammatory cytokines and depression. There is also extensive supporting data suggesting that anti-inflammatory treatments may be effective as adjunctive

treatment options for depression. There is however, a plentitude of studies that suggest the opposite, as discussed previously. More research is needed to validate the association between inflammation and depression prior to formulating any anti-inflammatory therapy to treat depression.

Implications for Nursing

Though the results of this literature review show a positive association between certain inflammatory markers and depression, more research is needed to ascertain the relationship before implementing new clinical guidelines for treatment. It is suggested that more randomized case control studies be completed, including a large sample size with controlling for external factors that may affect depression or systemic inflammation. There is an association between inflammation, cytokines, and depression, however there is not enough high-level literature looking at the directionality of this relationship.

In addition to completion of more randomized case control studies, it would be important to understand if depression precedes the elevation of inflammatory markers, or if inflammatory markers precede the depression through more longitudinal studies. By gaining this understanding it could be possible that inflammatory markers, such as cytokines, could be used as a biomarker to assess for a subtype of depression. With this assessment, anti-inflammatory treatment options could be considered along with the current recommended treatment guidelines.

Additionally, this literature review adds to the current research supporting the need for additional education and practice recommendations for nursing. Future nursing research should focus on better determining the efficacy of current treatments for depression and other factors that may be aiding in its pathophysiology, such as inflammation. With this research, new practice

and education recommendations could be put in place to provide better outcomes for patients. There is a plethora of current research supporting the role that inflammation plays in depression, as revealed by this review; however, more research is needed before relevant changes can be made to nursing education, practice, and policy.

Summary

In conclusion, this review adds to the literature supporting the association between inflammation and depression. Cytokines IL-6 and TNFα, along with pro-inflammatory marker CRP, were found to be elevated in subjects with depression compared to controls in all studies reviewed, excluding two. Several studies showed that with a reduction in depressive symptoms, the level of cytokines also decreased. In all literature reviewed, few studies looked at the directionality of the relationship between inflammation and depression. It is recommended that prior to implementation of treatment guidelines that more research is carried out looking at this specific relationship. It is also vital that the mechanism by which cytokines induce depression is also further considered and examined. By better understanding the mechanisms by which cytokines induce depression, better treatment opportunities would be possible in the future.

The relevance of this subject of study is imperative since so many people currently suffer from depression, even those being treated by the most current clinical guidelines. Almost 300 million people currently suffer from depression globally, and this number is expected to continue to rise. This has a tremendous impact on our society as a whole and it is vital that we treat it as such. More research on the etiology of depression and adjunctive treatment options, such as that with anti-inflammatory therapies, are important next steps in successfully treating depression.

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