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Food Intolerance in Patients with Depression

Victoria Gingrey
University of North Dakota

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Victoria Gingrey, PA-S

Department of Physician Assistant Studies, University of North Dakota

Contributing Author: Jay Metzger, MPAS, PA-C

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Abstract

Depression is a multifactorial condition affecting people worldwide. Medication is commonly prescribed for the treatment of depression, but some patients have difficulty finding a medication that is both effective and tolerable while others prefer to avoid medications all together. It has been suggested that dietary modification may reduce the depressive symptoms. As lifestyle changes may be difficult to maintain long term, determining specific foods to avoid for individual patients may improve adherence. A meta-analysis of 10 articles was performed. Articles were found using the electronic search databases PubMed and PsychInfo. Serology differences were appreciated between patients with depression and healthy controls. Some of these markers indicated higher potential for current or future disease, while others varied based on treatment response. Immunoglobulins are present at a much higher rate in patients with depression. Many studies found correlations between biomarkers and the prediction, diagnosis, or treatment of depression, though no study suggested specific guidelines for these purposes. Connections between food intolerance and depression were observed, but not enough data was found to evaluate whether the avoidance of food intolerances reduces depression symptoms when compared to anti-depressant medications.

Introduction

As of 2022, depression was the leading cause of disability worldwide (Belliveau et al., 2022). The Diagnostic and Statistical Manual of Mental Disorders (DSM) is a widely accepted guide used for the diagnosis of mental health conditions. At the time of this research, the DSM is on its fifth edition. According to the DSM-5, depressive disorders alter the affected person's ability to function due to both physical symptoms and changes in thinking. They experience sadness, emptiness, or irritability. Specific diagnosis varies based on duration, timing, and presumed cause of symptoms. Risk factors for these disorders are both environmental and genetic (American Psychiatric Association, 2013).

Low grade inflammation has been associated with depression (Kofod et al., 2021). It has been established that diets high in sugar, saturated fat, or certain meats have been linked to chronic diseases due to inflammatory properties (Belliveau et al., 2022). Therefore, dietary factors should be considered in the pathology and treatment of depression. Avoiding all inflammatory foods would result in a highly restrictive diet. What if it was possible to determine which specific foods cause inflammatory responses for a specific individual?

Food hypersensitivity refers to an adverse reaction in response to food; this encompasses both allergies and intolerances. Food allergies result from activation of immunoglobulin E, while food intolerance is an adverse reaction which may or may not be immune related. Many who experience food intolerance report digestive symptoms, but food intolerances have also been linked to extraintestinal symptoms (Aucoin & Bhardwaj, 2019). It is reasonable to consider that food intolerance may cause inflammation that may contribute to depression.

Statement of problem

All medications have side effects. The incidence and severity of these unintended consequences vary between patients and cannot be predicted. For patients, this can be a factor for medication hesitancy. In some cases, medications are chosen in hopes that specific side effects will occur and contribute to symptom relief, but this phenomenon is not guaranteed.

One factor that should be considered in any medical intervention is whether the proposed treatment provides symptomatic control or is curative. Through various mechanisms of action, antidepressant medications aim to affect the physiology of depression. These medications do not influence environmental factors. If or when the medication is discontinued, will the patient return to baseline? In a condition, such as depression, that involves both genetic and environmental factors, multifaceted treatment may be required.

Research Question

In patients with depression, does avoidance of food intolerances reduce symptoms when compared to anti-depressant medication?

Methods

A literature review was performed using the electronic search databases PubMed and PsychInfo. Keywords and MeSH terms were used to define a set of literature discussing depression in relation to inflammation. Keywords included depression, major depression, depressive disorder, food intolerance, food sensitivity, antidepressant drugs, antidepressant medications, inflammation, and inflammatory. After the filtering processes outlined below, 10 articles ultimately met relevance criteria.

Searches relating antidepressants and inflammation produced 243 results on PsychInfo. These results were then narrowed to include only peer-reviewed articles with human subjects

published in English within the past 5 years. Remaining articles were filtered to include only original studies with participants of at least 2 genders. Multiple studies were excluded due to use of non-medication antidepressant methods such as electroconvulsive therapy. Several studies were excluded due to specific study populations such as patients with specific autoimmune conditions or those that had undergone trauma (emotional or physical).

References relating to diet were narrowed to publication in the past 10 years. PubMed yielded 82 results and PsychInfo produced 14 sources. These results were also filtered to include only peer-reviewed articles with human subjects published in English. Several studies were excluded as they discussed diet as a covariate rather than a study parameter. Multiple studies were excluded due to specific study populations such as patients of a specific gender or those with specific autoimmune conditions. One article was found by suggestion of similar articles.

Literature Review

Inflammatory Markers in Patients with Depression

Toa et al. (2019) conducted a study with the goal of identifying early serological markers of depression. The serology of the study group, comprised of 184 adolescents diagnosed with depression based on the DSM-5, was compared with that of the control group, comprised of 184 age- and gender-matched healthy adolescents. All participants were enrolled following appointments at the General Hospital of the People's Liberation Army. Patients ranged in age from 14-20 years. Chronic disease was an exclusion criterion for the entire cohort, and patients with depression did not receive any form of antidepressant treatment before the study was conducted. The study evaluated three inflammatory markers: CRP, TNF-alpha, and histamine.

In this study, there was not a difference in average CRP levels between the study group and the control group ($p = .321$). No difference was found in average TNF-alpha levels either (p

= 0.408). Histamine levels were found to be significantly elevated in the group diagnosed with depression versus the control group ($p < 0.001$). To further evaluate this elevation, diamine oxidase, the metabolizing enzyme of histamine, was also measured, but no difference was found between groups ($p = 0.117$). The researchers sited evidence that chronically elevated histamine can increase permeability of the blood brain barrier (BBB). Thus, a central nervous system protein, S100 calcium-binding protien B (S100B), was measured to evaluate BBB leakage. The patients with depression had a significantly higher concentration of this protein in the blood stream than the control group ($p < 0.001$, Toa et al., 2019).

The study's exclusion of patients diagnosed with chronic diseases provides confidence in the relationship between depression and inflammatory markers. Participants were untreated at the time of the study, but it is not clear whether the lack of treatment is due to a new diagnosis or other reasons. It should be noted that the adolescents with depression presented for evaluation from various regions of China, while all control subjects were students in Beijing presenting for routine physicals. Regional factors may contribute to the results. Researchers attest to "similar social environments" but do not discuss how this was evaluated. Though the study groups were statistically gender-matched ($p > 0.05$, Toa et al., 2019), the group of patients with depression was 62% male, and the control group was 57% male. The ratio of male versus female participants may not be reflective of all populations.

Zainal and Newman published a study in 2021 evaluating whether inflammatory markers predicted future MDD prognosis of 945 subjects between the ages of 34 and 83. Participants of the 2004 Midlife Development in the United States study filled out the Composite International Diagnostic Interview Short Form of the Diagnostic and Statistical Manual of Mental Disorders—Third Edition—Revised (DSM-III-R) and the Childhood Trauma Questionnaire. Labs were then

drawn from participants to measure inflammatory markers (CRP, IL-6, and fibrinogen). Nine years later, participants filled out the updated DSM-IV form. The authors hypothesized that biopsychosocial variances would affect the predictive strength of inflammatory markers on MDD. Structural equation modeling was used to evaluate how well inflammatory markers predicted future MDD diagnosis or progression in 5 demographic groups: age, gender, income, childhood trauma, and number of chronic health conditions. Increased inflammatory markers predicted future MDD in participants under the median age of 45 better than those who were older ($p = 0.046$). Likewise, inflammation predicted future status of females more strongly than that of males ($p < 0.001$). MDD changes could be predicted in persons with 3 or more chronic conditions better than in those with less ($p = 0.050$). Inflammation was a better predictor in those with income levels at or below the median of the studied participants ($p < 0.001$). Higher inflammatory markers were more predictive of future MDD for those scoring at or above the median Childhood Trauma Questionnaire score ($p < 0.001$).

As participants were primarily recruited for the Midlife Development in the United States study, the authors were required to accept the demographics of that study's population. Inflammation was determined based off only 3 inflammatory markers, none of which were measured at the 9-year follow up. Gender was evaluated as a binary factor. Within the study population, participants below versus above the median values for age, income, and score of Childhood Trauma Questionnaire were compared, and persons with 3 or more chronic conditions were compared to those with 2 or less. These categories could have more intentional groupings.

Immunoglobulin Levels in Patients with Depression

The study done by Toa et al. (2019) measured immunoglobulin levels in addition to the previously discussed inflammatory markers. Quantitative IgE levels were measured to evaluate

type I hypersensitivity involvement. The group of adolescents with depression had a higher average IgE concentration when compared to the control group ($p < 0.001$). Qualitative IgG for 14 food-specific antigens was measured to evaluate type III hypersensitivity involvement. Of the group with depression, 89.67% of patients tested positive (> 50 KU/l) for at least one food-specific IgG compared to only 13.04% of the control group ($p < 0.001$). These results suggest that both IgE- and IgG-mediated hypersensitivities are involved in the onset of early depression.

Since the adolescents participating in the study that were diagnosed with depression hailed from all over the country of China, while all control subjects were students in Beijing, regional factors such as genetics and food access may contribute to the results. The sample size was large, but replication of the study in a different region of the country or of the world may yield different results.

Karakula-Juchnowiz et al. (2018) conducted a study comparing IgG levels of three subject groups: patients with major depressive disorder (MDD), patients with irritable bowel syndrome (IBS), and a group of healthy controls. None of the study participants were on a diet at the time of the study. Those in the MDD group had illness duration ranging from 0.5 to 22 years. IgG was detected in 64% of patients in the MDD group, in 46% of patients in the IBS group, and 19% of the healthy controls. IgG concentration across all groups revealed skewed distributions, therefore 3-way comparisons were evaluated using the Kruskal-Wallis analysis of variance test. If differences were detected, the Mann-Whitney test was used to evaluate differences between each 2-way combination of the 3 groups. The only 2-group comparison to reach statistical significance when comparing total IgG levels was MDD versus healthy controls ($p = 0.004$). The cohort was also asked to report frequency and severity of gastric complaints the week prior to evaluation using a 0-10 scale. Both the MDD and IBS groups had statistically more severe

complaints than the control group ($H = 16.25$, $p < 0.001$). Interestingly, higher IgG levels correlated with increased gastric complaints in the MDD group ($p < 0.05$; $R = 0.66$) but not the IBS or control groups.

The Karakula-Juchnowiz et al. (2018) study groups were small (22, 22, and 21 respectively), thus the researchers used ex-Gaussian statistics to analyze data. The sample sizes were likely small due in part to extensive exclusion criteria. To participate, patients could not have any inflammatory or infectious diseases or be on medications for such diseases. Those with substance abuse or mental handicap could not participate in the study. Patients in the depression and IBS groups were excluded if they had history of the other diagnosis. To avoid hormonal influences on results, the average age and the sex ratio was matched between the groups, only patients with normal body mass index (BMI) (18.5-30 kg/m^2) could participate, and pregnant and lactating patients were excluded. Although abnormal BMI was an exclusion criterion, BMI was not matched between groups (median BMI: MDD 28.6, IBS 22.8, healthy control 25.8). The depression group had a higher average BMI ($H = 9.59$, $p = 0.005$) and a lower rate of physical activity ($H = 7.77$, $p = 0.021$) than the IBS group. The researchers state that these differences were not statistically significant when analyzed, though the statistics were not included.

The efforts of Karakula-Juchnowiz et al. to avoid confounding factors were extensive, but the resultingly small sample sizes leave room for questions. A follow up study with a broader patient population would be beneficial as patients living with major depressive disorder often have comorbidities. Larger study groups with broader parameters may demonstrate a more accurate picture of the average patient.

Food-Specific Hypersensitivities

Toa et al. (2019) tested IgG levels against 14 specific food antigens. A patient's IgG level was considered positive for a specific antigen if above 50 KU/l. Of those diagnosed with depression, 89.67% tested positive for at least one food-specific IgG versus only 13.04% of the control group ($p < 0.001$). In both groups, IgG against egg was the most common food-specific antibody, but significantly more adolescents with depression tested positive than the control group (75% vs. 11.96% respectively, $p < 0.001$). IgG against milk (47.28% vs. 10.33%, $p < 0.001$), rice (11.96% vs. 1.63%, $p < 0.001$), tomato (11.96% vs. 1.63%, $p < 0.001$), corn, mushroom, soybean, chicken, crab, and codfish were also significantly higher in the study group (all $p < 0.04$). The only food-specific antigens that did not reach significance between groups were wheat ($p = 0.094$), shrimp ($p = 0.082$), and pork ($p = 0.521$). No one in the cohort was positive for IgG against beef.

Access to food is not discussed in this study beyond the researchers' claim of "similar social environments" between groups. While study participants diagnosed with depression hailed from all over the country of China, all control subjects lived in a single city. Thus, food options may vary between groups despite socioeconomic status. Additionally, dietary preferences can vary by region within a country. Differences in diet may or may not account for the significant differences in IgG levels to specific food antigens between the study groups.

Karakula-Juchnowicz et al. (2018) also tested food-specific IgG levels during their study comparing patients with MDD, patients with IBS, and healthy control participants. Recall that total IgG levels were significantly higher in the MDD group versus healthy controls ($p = 0.004$). Compared to the healthy control group, patients with MDD have higher average concentration of IgG against broccoli ($p = 0.039$), celery ($p = 0.019$), horseradish ($p = 0.024$), garlic ($p = 0.015$),

gluten ($p = 0.025$), wheat ($p = 0.043$), rye ($p = 0.032$), and dairy ($p = 0.019$). Compared to the IBS group, patients with MDD have higher average concentration of IgG against gluten ($p = 0.010$) and sunflower seed ($p = 0.038$). Neither the IBS group nor the healthy control group had statistically higher levels of total or specific IgG when compared to the other groups.

Though the sample sizes of this study were not large, they do suggest elevation of immunoreactivity in MDD patients. As the study was done cross-sectionally, conclusions cannot be made regarding whether inflammation contributed to MDD onset or vice versa. As the study was conducted in Poland, specific food antigens tested were selected based on foods of that culture. Again, replication of the study in a different region of the country or of the world may yield different results due to antigen exposure.

Jonsson et al. (2021) conducted a prospective study following children born in Stockholm, Sweden between 1994 and 1996. Parents were interviewed when the children were 2 months old as well as when children were 1, 2, 4, 8, 12, and 16 years or age. Of the 4089 children in the original cohort, 78% (2990) responded to the final follow-up. Family history, socioeconomic status, and environmental exposures were the topics of the first interview. Subsequent interviews reviewed these topics and asked if the child had any reactions to specific foods or was avoiding specific foods due to allergy testing or previous reactions. Reactions included gastrointestinal distress, asthma, itching, urticaria, swelling, and unconsciousness. Parents of 650 (22%) children reported food-specific reactions. Researchers used this as their definition of food hypersensitivity, thus this group of adolescents became the study group. At 16 years, the children were interviewed using the EQ-5D questionnaire to determine self-reported quality of life (no problems, some problems, or extreme problems) in 5 categories (self-care, mobility, usual activities, pain, and anxiety or depression). Adolescents defined to have food

hypersensitivity reported more problems than those without regarding anxiety/depression ($p = 0.007$), pain ($p < 0.001$), and usual activities ($p = 0.04$). Regardless of food hypersensitivity, reported quality of life was lower in females, smokers, overweight adolescents, and children of parents with lower socioeconomic status. Females reported more pain and anxiety/depression than males (both $p < 0.001$). Smokers reported more difficulties in usual activities as well as more anxiety/depression than non-smokers (both $p < 0.001$). Overweight adolescents reported reduced mobility ($p = 0.005$) and increased pain ($p = 0.006$). Children of parents with lower socioeconomic status reported more pain than those of parents with higher status ($p = 0.02$). After adjusting for differences in gender, weight, socioeconomic status, and smoking, significant difference remained between pain ($p = 0.007$) and anxiety/depression ($p = 0.05$). To reduce the risk that anxiety caused increased reporting of food hypersensitivity symptoms, quality of life scores for adolescents taking antianxiety, antidepressant, and migraine medications were compared between those with and without food hypersensitivity, but no difference was found ($p = 0.71$). Severe symptoms (rash over the majority of the body, difficulty breathing, unconsciousness) did not affect quality of life when compared to less severe reactions (mobility $p = 0.62$, self-care $p = 0.30$, usual activities $p = 0.89$, pain $p = 0.64$, anxiety/depression $p = 0.39$).

The most commonly reported hypersensitivities included peanut (41.5%), milk (31.2%), wheat (4.6%), egg (4.3%), and fish (2.9%). The hypersensitivities associated with the lowest self-reported health scores were milk ($p = 0.03$) and wheat ($p = 0.04$). Of the study population, 83% (2477) subsequently had blood drawn to evaluate for IgE against peanut, milk, wheat, egg, fish, and soy (with levels ≥ 0.35 kUA/L considered positive). Within the food hypersensitivity group, no differences were found in quality of life between those that were positive or negative

for IgE (mobility p = 0.10, self-care p = 0.52, usual activities p = 0.70, pain p = 0.81, anxiety/depression p = 0.65, Jonsson et al., 2021)).

The final study population had a lower ratio of males (50.5% vs. 49.1%), higher socioeconomic status (parental white-collar workers 82.7% vs 84.2%), and lower rate of parental smoking (21.0% vs. 20.0%) than that of the original cohort. As discussed, gender, socioeconomic status, and adolescent smoking affected quality of life responses. Of the 650 adolescents defined by the researchers to have food hypersensitivity, 280 (43%) denied the reactions reported by their parents. It is unclear whether the number reported by the parents was cumulative over the 6 interviews (therefore encompassing their children's entire lives) or based on the most recent interview. The adolescents only had one interview and may not have been aware of food reactions they had early in life those had resolved. While five common foods were chosen for IgE testing, symptoms against other foods were included in the definition of hypersensitivity. As the cohort was selected from a single city in Sweden, replication of the study in a different region of the country or of the world may yield different results due to genetics and/or antigen exposure.

Anti-Inflammatory Properties of Antidepressants

A study designed by Haroon et al. (2018) evaluated whether a relationship existed between inflammatory markers in patients with MDD and the number of failed antidepressant medication trials for the current depressive episode. Recruitment campaigns for the study occurred through television, radio, newspaper, and internet advertisements. Subjects were required to be 21 to 65 years old and currently experiencing a depressive episode (as defined by the DSM-IV). Participants were excluded if they had taken psychotropic medications in the past 4 weeks, had suicidal ideation, had a previous diagnosis of any other psychiatric disease, or had any comorbid disease that affected the immune system. Depressive symptoms were measured

using the Hamilton Depression Rating Scale (HAM-D). The Massachusetts General Hospital Antidepressant Treatment Response Questionnaire (MGH-ATRQ) was used to assess prior treatment history as well as to define an "adequate" trial of antidepressant treatment (at least 6 weeks at or above the recommended initial dose of a given medication). Patients were divided into four groups based on number of adequate medication trials for the current depressive episode. Patients not treated with medication were placed in treatment category 0, those who tried only one medication made up category 1, category 2 was comprised of those who had taken two medications, and those that had tried three or more medications were placed in treatment category 3. Four inflammatory markers were significantly elevated in patients that had undergone more medication trials: TNF (3 vs. 0 [$t = 2.87$, $p = 0.03$] and 3 vs. 1 [$t = 2.82$, $p = 0.03$]), sTNF-R2 (3 vs. 0 [$t = 3.43$, $p = 0.005$] and 3 vs. 1 [$t = 3.37$, $p = 0.006$]), IL-6 (3 vs. 1 [$t = 3.10$, $p = 0.01$] and 2 vs. 1 [$t = 2.94$, $p = 0.02$]), and CRP (3 vs. 1 [$t = 2.17$, $p = 0.03$] and 2 vs. 1 [$t = 2.51$, $p = 0.014$]). There was no significant difference between groups in regards to age ($p = 0.10$), gender ($p = 0.72$), or education ($p = 0.49$). BMI directly coincided with levels of many inflammatory markers (CRP, IL-6, IL-1beta, IL-1ra, and sTNF-R2 [all $p < 0.001$]) but was not different between treatment categories ($p = 0.40$). Race was a significant background variable, with African-Americans undergoing less medication trials than Caucasians. Patients were identified as either black (54.1%) or white (45.9%). Using this binary classification system, patients identifying as black made up 59.6% of treatment category 0, 75% of category 1, 46.2% of category 2, and 18.8% of category 3.

Recruitment relied on participant access and attention to media, which not all eligible subjects might have. This study was performed cross-sectionally. For this particular hypothesis, a longitudinal study would better demonstrate how many treatment trials were required to reach

remission. The sample sizes were relatively small. Researchers used a prospective study design, which is preferred, but larger study populations are required for this method as sample sizes are determined by outcome and are therefore less predictable than assigned groupings. Most covariates were insignificant, but race was a significant demographic factor, the reason for which was not explicitly explored.

Navinés et al. (2022) conducted a study evaluating the changes of inflammatory markers throughout 8 weeks of antidepressant medication therapy. A total of 31 patients were recruited from the hospital clinic psychiatry and psychology department at the University of Barcelona, 27 of which completed the study. All met the DSM-IV-R criteria for MDD. Exclusion criteria included age over 70, comorbid psychiatric disorder, inflammatory condition, and current use of antidepressant medication. Serum was obtained to measure S100B, CRP, and HDL-C. The Montgomery and Asberg Depression Rating Scale (MADRS) was used to quantify depressive symptoms and the Global Assessment of Functioning (GAF) scale was used to quantify daily function. Based on individual patient-provider decision making, patients were then started on either escitalopram or sertraline. Revaluation of symptoms and serum was performed at 4 weeks and at 8 weeks. Patients were categorized as responders at follow up visits if MADRS score decreased by 50% or more from baseline. If not, patients were considered non-responders. Medication dose was increased for non-responders at 4 the week visit. More response was seen at the 4-week visit (25 patients, 74%) than at the 8-week visit (21 patients, 63%).

The only inflammatory marker that correlated with clinical findings at baseline was an inverse relationship between CRP levels and GAF scores ($r = -0.487$, $p = 0.006$). At week 4, there was significant difference between all baseline biological markers and treatment response. Higher S100B levels at baseline correlated with increased responsiveness to medication ($r =$

0.451, p = 0.011), while the opposite was true for CRP levels (r = -0.402, p = 0.025) and HDL-C levels (r = -0.450, p = 0.013). At 8 weeks, baseline comparisons of S100B (r = 0.044, p = 0.022) and HDL-C (r = -0.401, p = 0.42) remained predictive of treatment response, while CRP levels did not. Furthermore, patients with baseline S100B levels at or above the median of the study population had significantly lower MADRS scores at both 4 (p = 0.020) and 8 (p = 0.006) week follow-ups. Co-variants were analyzed, and no significant difference was found between treatment response and gender (p = 0.516), age (week 4 p = 0.421, week 8 p =0.412), BMI (week 4 p = 0.904, week 8 p = 0.978), comorbidities (p = 0.055), tobacco use (p = 0.580), or SSRI used (p = 0.239, Navinés et al., 2022).

All patients were recruited from a single clinic in Spain in a limited time frame. Geographical location, local events, seasonal changes must be considered as possible co-variants. The study lacked a control group, used a small sample size, and used only one class of antidepressant medication.

Kofod et al. (2021) conducted a study monitoring inflammatory markers and depressive symptoms over the course of 10 years. Ninety patients diagnosed with depression based on the Schedules for Clinical Assessment in Neurology interview were recruited from Aarhus University Hospital in Denmark. At time of enrollment, all patients were at least 18 years of age, were not on mood-altering medications, and did not have personal history of schizophrenia or a first-degree relative with history of schizophrenia. After baseline measurements of depressive symptoms (using HAM-D, MADRS, and Beck Depression Inventory [BDI]) and a blood draw, patients were started on either escitalopram or nortriptyline. Patients were randomly assigned to a group unless they had previously experienced adverse effects, previously did not respond, or

had contraindications to one of the medications, in which case they were assigned to the opposite group. Lab draws and depression rating scales were repeated at 8, 12, and 26 weeks.

During the trial period, 63.3% of patients responded to medication (MADRS score decreased >50%) and 47.8% of patients achieved remission (MADRS score <10). There was no difference in responsiveness or remission when comparing escitalopram versus nortriptyline or the covariates of age, sex, smoking, BMI, or treatment naivety (all $p > 0.1$). While 17 of the 27 inflammatory markers decreased during the trial, no significant differences were found in regards to inflammatory markers and medication response. No inflammatory marker was significantly correlated with overall MADRS, though some showed correlation with depressive symptoms. There were 16 inflammatory markers associated with mood disruptions (all $p \leq 0.05$), 12 associated with cognitive concerns (all $p \leq 0.05$), 12 associated with neurovegetative states (appetite changes, energy level, pain, sleeping problems) (all $p \leq 0.04$), and 8 significantly associated with suicidality (all $p \leq 0.04$). Of these symptom categories, 2 cytokines (IL-15 [all $p \leq 0.0009$] and IL-7 [all $p \leq 0.002$]) demonstrated significance across all categories, 3 inflammatory markers (eotaxin-1, MIP-1beta, and IL-4) demonstrated significance across 3 of 4 categories, and 3 inflammatory markers (IL-13 [all $p > 0.13$], FGF basic [all $p > 0.14$] and MIP-1alpha [all $p > 0.15$]) did not demonstrated significance in any category. One inflammatory marker (IL-9) was significantly higher at baseline in patients that subsequently achieved remission than in those that did not ($p = 0.01$), with all other associations being insignificant ($p > 0.05$). By the 10-year follow-up, 22 participants (24.4%) had been hospitalized for depression, with an additional 7 (7.8%) admitted at a psychiatric hospital with other diagnoses. No correlation was found between risk of psychiatric hospitalization and inflammatory markers at any point during the study (all $p > 0.1$, Kofod et al., 2021).

All patients were from a singular region in Denmark and smoking was the only lifestyle factors collected. These are co-variables that can factor into both inflammation and depression. Serum was collected between 2004 and 2007, frozen, and tested in 2019. This was done to allow testing of all samples using the same batch of testing kits, but the long and variable storage time may have affected sample results. Some laboratory data was missing as some sample results were outside measurable range and not all patients provided serum at all time points (50% of participants provided serum samples at all time points; the smallest sample size was 50 patients at week 26). The 10-year data was collected via a database of hospital visits in Denmark dated between 32-months and 10-years after study initiation. Direct contact was not made with study participants, and neither depression scales or serum levels were documented at that time. This may have allowed for increased compliance but is inconsistent with the measurement methods used earlier in the study.

Anti-Inflammatory Diets in Patients with Depression

Belliveau et al. (2022) conducted a study evaluating the relationship of dietary habits and depression. An anonymized survey was sent to employees and students of Princeton Community Hospital and West Virginia School of Osteopathic Medicine. There were 631 respondents. The survey included mood questions in the form of the Patient Health Questionnaire-9 (PHQ-9), in which higher scores indicate increased severity of depression. The survey also included dietary questions in the form of the Empirical Dietary Inflammatory Index (EDII), which estimates an individual's diet effect on inflammatory markers. In regards to the EDII, higher scores indicate increased inflammatory potential. Foods considered to be pro-inflammatory earn positive points and include processed meat, red meat, low oil fish, eggs, tomatoes, processed grains, and sugar-sweetened beverages. Those considered anti-inflammatory earn negative points and include oily

fish, leafy green and dark yellow vegetables, fruit juice, coffee, tea, and alcoholic beverages. Scores are summated based on frequency of weekly consumption. Results showed significant correlation between high PHQ-9 scores and high EDII ($F = 18.32$, $p < 0.0001$) even after adjustment for statistically significant co-variants (gender [$F = 8.09$, $p = 0.0003$], physical exercise [$F = 4.81$, $p = 0.0026$], spiritual exercise [$F = 8.91$, $p < 0.0001$], and previous psych diagnosis [$F = 58.79$, $p < 0.0001$]).

The study population was selective, with all respondents being medical professionals or medical students in West Virginia. Participants completing the survey had the opportunity to be entered for a gift certificate drawing, providing incentive, though this was not guaranteed. The study was conducted cross-sectionally and consisted of only self-reported questionnaires. The study population was disproportionately female (75%). Students, a sub-population with unique stressors, also comprised a large portion of the respondents (44%).

Aucoin and Bhardwaj (2019) published a case study of a patient who opted to treat depression with lifestyle changes rather than pharmaceutical medications. The 34-year-old woman met DSM criteria for MDD and had been living with depression for 22 years. She was treated with venlafaxine between the ages of 20 and 29, but she did not feel this helped much. Dose increases had caused side effects including headaches and vomiting, which lead her to discontinue the medication. The patient had participated in counselling as well as cognitive behavioral therapy, which were reported to be moderately helpful. Personal history included childhood trauma and prior substance use disorder. At baseline, patient reported constipation (1-2 bowel movements per week) and initiation insomnia (averaging 2 hours to achieve sleep). Mild facial acne was the only physical finding.

The patient was started on a hypoallergenic diet. Foods that she was instructed to avoid included dairy, wheat, eggs, peanuts, soy, coffee, alcohol, sweeteners, tomatoes, potatoes, peppers, and corn. After 2 weeks, the patient reported improved mood, increased energy, and more frequent bowel movements (every other day). After 3 weeks of the hypoallergenic diet, she was encouraged to reintroduce one food into her diet every 3 days. If an adverse reaction was noted, the food should be avoided indefinitely. During respective reintroduction phases of dairy and gluten, the patient reported headaches, abdominal discomfort, and bloating. Within 24 hours of dairy consumption, the patient also reported increased sadness, including episodes of crying. She denied concurrent events or changes that contributed to these symptoms. The patient returned for follow up every 3 weeks for 2 years. During that time, she discontinued the dietary restrictions 5 times. Each time, she reported constipation, headaches, and decreased mood. She subsequently restarted the diet and noted improvement in these symptoms. An IgG test later revealed that the patient had hypersensitivity to wheat, yeast, and casein (a dairy protein).

As a case study, this report outlines the experience of only one patient, so no population inferences can be made. Objective assessment tools were not used to monitor the patient's symptoms throughout the course of treatment. The resulting subjective symptom data cannot be validated. Despite these weaknesses, the study did have strengths that should be considered. Diet was the only change implemented upon initial treatment. Other lifestyle changes were delayed until after the reintroduction phase was complete. Therefore, we can be confident that the patient did perceive symptom improvement based on dietary changes alone. Arguably, the biggest strength of the study is that an IgG test confirmed the patient's reaction to wheat and dairy products. The fact that this was performed after the study prevented bias during the reintroduction phase and gave the patient further motivation to continue dietary restrictions.

Parker and Watkins (2002) published a case study of a patient who trialed an elimination diet following multiple failed trials of psychotropic medications. The 27-year-old man reported both depression and anxiety symptoms that were persistent despite 7 years of cognitive behavioral therapy and medication trials. He had trialed 13 prescription medications in 9 drug classes in addition to 3 over the counter supplements. Many of these medications decreased his anxiety, but they also caused nausea, light-headedness, and worsened depression after 2 days of use. His symptoms continued to worsen, and now included constipation, diarrhea, fatigue, and myalgia. Due to this, he was no longer able to maintain his job.

An allergy specialist started the patient on the elimination diet. He reported mood improvement after one month and maintained the diet for 2 months. At that point, a reintroduction trial was initiated. Twelve capsules containing suspected allergens were scheduled in a double-blind fashion. After taking the first capsule, all symptoms returned within days. Reintroduction was aborted when symptoms did not improve after one week. It was then revealed that the capsule had contained acetylsalicylic acid, a chemical known to cause many adverse food reactions. At a one-year follow up, the patient had maintained the elimination diet and returned to employment. Residual symptoms were transient and mild.

As a case study, this report outlines the experience of only one patient. No objective assessments were used to quantify the patient's subjective experience. Though the patient did trial many medications, the quantity of failed medications is concerning for the quality of each medication trial. The patient's persistence with the strict elimination diet does restore some of this credibility. Later review of family history revealed that the patient's mother, her father, and her brothers also followed unspecified modified diets for unspecified reasons for up to 50 years.

Discussion

Current literature regarding inflammatory markers suggests correlations to clinical symptoms. The impact of these markers on diagnosis or treatment is less clear.

In the studies evaluated, the most commonly evaluated inflammatory marker was CRP. Though adolescents with a diagnosis of depression did not have elevated CRP levels when compared to their peers ($p = 0.321$, Toa et al., 2019), higher levels were predictive of future depressive symptoms in patients under 45 ($p = 0.046$, Zainal & Newman, 2021). High baseline CRP correlated with decreased daily function ($r = -0.487$, $p = 0.006$) and lower responsiveness to anti-depressant medications at 4 weeks of treatment ($r = -0.402$, $p = 0.025$, Navinés et al., 2022). Post-treatment CRP levels were lower in patients who had been on only one anti-depressant medication when compared to those that had tried more (Haroon et al., 2018).

TNF was measured in two cross-sectional studies. One study measured levels before treatment and the other evaluated levels after treatment. In the pre-treatment study, no significant difference in TNF was found between patients with depression versus those without ($p = 0.408$, Toa et al., 2019). Post-treatment TNF levels were higher in patients who had tried at least 3 anti-depressant medications when compared to those that tried only one medication ($p = 0.006$) or had not tried medication therapy ($p = 0.005$) (Haroon et al., 2018).

Two studies measured S100B to evaluate BBB integrity. As a central nervous system protein, high levels of S100B in blood serum indicate BBB leakage (Toa et al., 2019). Prior to treatment, patients diagnosed with depression had higher levels of S100B when compared to controls ($p < 0.001$, Toa et al., 2019). At baseline, no clinical findings correlated with S100B levels, but higher S100B levels were linked to increased responsiveness to antidepressant medications (Navinés et al., 2022).

A variety of interleukins were evaluated between the reviewed publications. In a prospective study, inflammatory markers, including IL-6, tended to be predictive of future MDD if a patient was female, less than 45 years of age, had 3 or more chronic conditions, had experienced childhood trauma, and/or received lower income (Zainal & Newman, 2021). Haroon et al. (2018) found that patients who had tried two or more antidepressant medications had higher post-treatment levels of IL-6 when compared to those that had tried only one medication. Interestingly, the opposite was true of IL-9, as higher baseline levels were predictive of remission while taking antidepressant medications ($p = 0.01$, Kofod et al., 2021). Patients with higher baseline IL-7 and/or IL-15 reported more depressive symptoms such as mood disruptions, cognitive concerns, neurovegetative symptoms, and suicidality ($p \leq 0.002$ and $p \leq 0.0009$ respectively, Kofod et al., 2021).

Cumulative results from current literature suggest that both type I (IgE-mediated) and type III (IgG-mediated) hypersensitivity reactions occur more frequently in patients with depression. It should be considered that each study measured immunoglobulins at only one point in time, so we cannot be certain whether food intolerance leads to depression, depression leads to food intolerance, or if a different pathway predisposes persons to both depression and food intolerance.

Type I immune responses are mediated by IgE (Toa et al., 2019). Toa et al. (2019) found that adolescents with depression had significantly higher concentrations of IgE than their peers ($p < 0.001$, Toa et al., 2019). Jonsson et al. evaluated the clinical significance of IgE hypersensitivities in this population. Adolescents with anecdotally reported food reactions reported more anxiety and depression than those without ($p = 0.05$), though anxiety and depression were unrelated to the severity of reactions ($p = 0.39$). Subsequent serological

evaluation revealed IgE in 29% of the group reporting food reactions, but presence of IgE did not affect anxiety or depression scores ($p = 0.65$, Jonsson et al., 2021). IgG was not measured in that study and should be considered as one of the possible explanations for the discrepancy.

Type III immune responses are mediated by IgG (Toa et al., 2019). In one study, 89.67% of adolescents with depression tested positive for at least one food-specific IgG compared to only 13.04% of their peers ($p < 0.001$, Toa et al., 2019). In a study evaluating an adult population, IgG against tested food antigens was detected in 46% of patients with MDD compared to 19% of healthy participants ($p = 0.004$). The MDD group had statistically more severe complaints than the control group ($H = 16.25$, $p < 0.001$). Additionally, higher IgG levels correlated with increased gastric complaints ($p < 0.05$; $R = 0.66$, Karakula-Juchnowicz et al., 2018). These studies agree that IgG levels are elevated in patients diagnosed with MDD. Unlike the study conducted by Toa et al. (2019), in which patients were tested for immunoglobulins prior to treatment, the patients participating in the Karakula et al. (2018) study were being treated with prescription antidepressant medications at the time of the study. This indicates that IgG continues to be elevated throughout the course of MDD if no dietary changes are implemented.

Two of the reviewed studies measured IgG against specific food antigens. Performed in different countries, the antibodies tested varied based on local cuisine, though two food groups overlapped between the studies. When compared to healthy controls, both studies found significantly elevated IgG against milk in patients diagnosed with depression when compared to those without ($p < 0.001$, Toa et al., 2019) ($p = 0.019$, Karakula-Juchnowicz et al., 2018). Wheat IgG was significant in one study ($p = 0.043$, Karakula-Juchnowicz et al., 2018), but not the other ($p = 0.094$, Toa et al., 2019). In regards to regional grains, Toa et al. (2019) found significantly elevated IgG against rice ($p < 0.001$) in the Chinese study group, while Karakula et al. (2018)

noted significantly elevated IgG against rye ($p = 0.032$) in the Polish study group. Regional vegetables inducing higher rates of IgG production in patients with depression included tomato ($p < 0.001$), corn ($p = 0.001$), and mushroom ($p = 0.006$) in the Chinese study (Toa et al., 2019), and broccoli ($p = 0.039$), celery ($p = 0.019$), and horseradish ($p = 0.024$) in the Polish study (Karakula-Juchnowicz et al., 2018).

There is a potential that identical studies conducted in different regions of the world would produce different results. Immune reactivity is multifactorial, but antigen exposure is required for immunoglobulin formation. A standardized immunoglobulin panel completed in different regions of the world might reveal innate human allergens, but individuals naive to an antigen may skew results. In this case, regional studies may be more accurate than global studies in predicting potential hypersensitivities.

Three of the reviewed studies directly evaluated the effects of diet on depression symptoms. Belliveau et al. (2022) used the EDII to define the foods that have the most inflammatory potential. The study found that participants consuming a higher volume of inflammatory foods had higher PHQ-9 scores ($p < 0.0001$). Two case studies evaluated dietary modification as treatment for depression. Both patients were instructed to avoid all common food allergens for a period of time before slowly reintroducing one food at a time. One patient, who had failed multiple trials of antidepressant medications, had such a severe reaction to reintroduction that he preferred to stay on the full elimination diet. He maintained this for at least one year and had marked functional improvement of depressive symptoms (Parker & Watkins, 2002). The other patient, who preferred non-medicated antidepressant treatments, was able to identify 2 food groups, dairy and gluten, that caused both physical and mental symptoms. Over

the 2 years that followed, she did partake in the offending food groups a handful of times, but subsequently re-eliminated them due to symptoms (Aucoin & Bhardwaj, 2019).

All three studies were based on generally accepted inflammatory diet guidelines rather than testing individual patients for specific reactions. Immunoglobulin activity should not be ruled out since inflammation is immune mediated. In the case study published by Aucoin and Bhardwaj (2019), the patient was subsequently tested for immunoglobulins, which confirmed the subjectively determined hypersensitivities. Thus, if specific allergen testing is not accessible, it is possible, in at least some cases, to identify sensitivities without laboratory evaluation.

Conclusion

The biomarkers evaluated by the reviewed studies vary, but many found correlations with the prediction, diagnosis, and treatment of depression. No study suggested a specific laboratory level to guide prediction, diagnosis, or treatment of depression.

There was not enough data found to evaluate whether the avoidance of food intolerances reduces depression symptoms when compared to anti-depressant medications. This is in part due to the lack of cohort studies specifically researching dietary management of depression. Nonetheless, connections between available data sets were observed. The cumulation of data evaluated points toward the potential for dietary management of depressive symptoms. Dedicated studies are needed to evaluate the efficacy of personalized diet plans in depression.

Application for clinical practice

Many patients with depression trial a variety of anti-depressant medications until finding one that is effective and tolerable. Patients who have failed multiple medications and those who are strongly opposed to taking medications should be informed of the possibility of diet control. Though testing of food-specific immunoglobulins is not yet readily available, information on

elimination and reintroduction of food is. This should be an option for patients not requiring acute medical intervention for depressive symptoms.

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