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REVIEW OPEN ACCESS

Fecal Calprotectin as a Biomarker of Depression Severity: A Systematic Review

Kuljeet K. Chohan, BSc Student [1]*^, Bharat Duggal, BSc Student [2]^

[1] Department of Psychology, University of Calgary, Calgary, Alberta, Canada T2N 1N4
[2] Department of Kinesiology, University of Calgary, Calgary, Alberta, Canada T2N 1N4

*Corresponding Author: kuljeet.chohan@ucalgary.ca
^All authors were equal contributors to this study.

Abstract

Introduction: Depression is a debilitating mental health condition. Although the underlying pathophysiology of depression is poorly understood, emerging evidence suggests that the gut-brain-immune axis may contribute to depressive symptoms. Recent literature has established that depression is associated with systemic low-grade inflammation. According to the leaky-gut hypothesis, this systemic inflammation is thought to be caused by increased permeability—a by-product of mucosal inflammation. Accordingly, some research has demonstrated that fecal calprotectin (FC)—a marker of mucosal inflammation—is positively associated with depressive symptoms. However, with some research showing no correlation between the two, the literature has a lack of consensus on the topic. The aim of the current systematic review was to clarify the association between FC and depression.

Methods: A search was conducted in Ovid MEDLINE, Embase, and APA PsycInfo using MeSH terms related to fecal calprotectin and depression. All English studies with human participants were screened for eligibility by two individual raters, excluding case studies and review papers. Selected articles were subsequently used in the data extraction to look for relevant study characteristics and their findings regarding the correlation between fecal calprotectin and depression. Additionally, the JBI tool was used to assess risk of bias.

Results: A total of 7 articles were included in the study, comprising 1184 patients. The review found that there is no consensus on whether calprotectin and depression are correlated; therefore, no evidence suggesting utility of calprotectin as a biomarker of depression was found.

Discussion: Despite the conflicting findings of the study, there is still some evidence to suggest that calprotectin could be useful as a biomarker. Some of the included studies found that the time of sample collection in relation to the ranking of depression symptoms has an effect on the degree of correlation.

Conclusion: This study found that fecal calprotectin is a weak biomarker of depression and is impractical in the general population due to the collection method. Alternatives include serum calprotectin and markers of neuroinflammation. Other studies looking at the role of salivary biomarkers in depression may prove to be promising.

Keywords: calprotectin; depression; biomarker; diagnosis; inflammation; gut-brain-immune; gut-brain

Introduction

Background

Depression is estimated to affect 280 million people worldwide [1]. Globally, depression accounts for the largest share of the total disease burden and is the leading cause of disability, incurring significant economic and public health costs [1]. Standard pharmacological treatments and complementary therapies such as psychotherapy are available to depression patients, but the needs of many are still unmet, with treatments being ineffective for a sizable clinical population [2]. One challenge associated with the development of effective therapies is the limited current understanding of depression pathophysiology. Though the precise biological mechanisms that cause depression are still largely unknown, a new perspective suggests that the gut-brain immune axis may underly depression pathophysiology, creating the potential for novel treatment options [3,4].

The gut-brain-immune axis represents a complex bidirectional communication network involving the gastrointestinal tract, the central nervous system, and the immune system. This axis plays a pivotal role in maintaining homeostasis and influencing various physiological processes, including those related to mental health. Research has increasingly implicated the gut-brain-immune axis in the pathophysiology of depression [5]. The gut microbiota, comprising trillions of microorganisms residing in the gastrointestinal tract, has emerged as a key player in this axis. Interactions between the gut microbiota and the central nervous system—facilitated by bidirectional

communication through neural, hormonal, and immunological pathways—have been shown to influence mood, behavior, and cognitive function [6]. Dysregulation of the gut microbiota, known as dysbiosis, has been linked to alterations in the immune response and systematic inflammation, which are associated with depressive symptoms [7].

Recent literature has established that low-grade systemic inflammation accompanies depression, potentially caused by a leaky gut (coined the "leaky gut hypothesis") [8]. Normally, the intestinal epithelium is responsible for ensuring that the enteric nervous system and systemic circulation are not infiltrated by pathogens in the gastrointestinal (GI) tract, such as harmful bacteria or lipopolysaccharides. However, when such substances cross the mucosal barrier of the intestine, they cause the release of pro-inflammatory cytokines that are upregulated with depression, such as tumour necrosis factor-alpha (TNF-a) and interleukin-6 (IL-6) [9]. These increases in intestinal permeability are also associated with mucosal inflammation [10]. It is unknown whether these inflammatory responses are a cause or effect of depressive symptoms. In either case, detecting the deterioration of the intestinal mucosa through mucosal inflammation may be of interest when considering biomarkers of depression.

Of particular interest in this study is fecal calprotectin. Calprotectin is a calcium- and zinc-binding protein (S100A8/A9 homodimer) present in human neutrophils and macrophages [11]. Following gut inflammation, calprotectin is released by neutrophils that migrate into the intestinal lumen and is excreted in the stool. Because the presence of calprotectin in the feces is directly proportional to neutrophil migration in the GI-tract, it can be used as a biomarker for mucosal inflammation. Unlike other common laboratory inflammation measures—like C-reactive protein, TNF-a, and IL-6—fecal calprotectin (FC) levels are specific to inflammation in the GI tract and are relatively unaffected by systemic inflammation. In addition to being a specific biomarker for mucosal inflammation [12], FC is also associated with intestinal permeability [13], which as mentioned, may be linked to depression. Iordache and colleagues [14] had recently found that FC concentration has moderate positive correlations with depression severity and can be used diagnostic tool for detecting depression. However, conflicting findings from other studies [15] highlight the need for a comprehensive review of the topic.

The present review aimed to determine whether FC levels are associated with scores on validated major depressive disorder (MDD) symptom questionnaires. Since FC levels are specific to mucosal inflammation and related to gut permeability, clarifying the relationship between FC and depressive symptoms contributes to our understanding of how the gut-brain-immune axis interacts with neuropsychologic function.

Research Question

Can fecal calprotectin be used to detect the presence and/or severity of depression?

Methods

Search Strategy

This study was reported in accordance with the updated Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement. The search was conducted in Ovid MEDLINE, Ovid PsycINFO, and Ovid EMBASE, encompassing a broad variety of terms related to calprotectin and depression (Table 1). No restrictions were applied at this point.

Table 1. Complete Search Strategy, as inputted into Ovid MEDLINE, Embase, and APA PsycInfo in October 2023

Set	Search Statement
1	exp Depression/ or depress*.mp. or exp Depressive Disorder, Major/
2	calprotectin.mp. or exp Leukocyte L1 Antigen Complex/
3	depression.tw,kf,rn.
4	depress*.tw,kf,rn.
5	Major Depressive Disorder.kw,kf,rn.
6	calprotectin.tw,kf,rn.
7	Leukocyte L1 Antigen Complex.tw,kf.
8	1 or 3 or 4 or 5
9	2 or 6 or 7
10	8 and 9

Note: This search strategy encompassed a range of MeSH terms involving depression and fecal calprotectin where applicable.

Inclusion and Exclusion Criteria

Studies conducted in English with human participants were included. Eligibility was confined to those studies measuring depression using any validated survey or questionnaire, and which reported having conducted either: (1) a comparison of depression symptoms/outcomes between groups that have been stratified using FC or (2) a correlation between FC and depression.

Table 2. Inclusion and Exclusion Criteria for Study Selection

Inclusion	Exclusion
1. English 2. Used a validated measure of depression 3. Reported conducting a comparison of depression scores/symptoms between groups stratified by FC or reported a correlation between FC and depression scores/symptoms	1. Case-study design 2. Review study design 3. Non-human participants 4. Participants with neurological, infectious, or autoimmune diseases other than IBD 5. Participants with reported severe psychiatric disorders

Abbreviations: FC: fecal calprotectin; IBD: inflammatory bowel disease.

Study Selection and Data Extraction

Article title, abstract, and full-text screening were conducted by two authors (KC and BD) using the Covidence software [16]. Where there were conflicts on study eligibility, authors had to reach a consensus before making a final decision. Data from the studies that met inclusion criteria was extracted using a standard extraction form which included information on study identifiers, population descriptors, treatments, and outcomes of interest. References of relevant but excluded review articles and all included articles were manually searched. Citation tracking was also used to identify other potential studies in Ovid MEDLINE, APA PsycINFO, and Embase.

Results

Study Selection

The study selection process is summarized in Figure 1. The search strategy generated a total of 442 articles – 70 of which were automatically screened out by the Covidence software as duplicate articles retrieved from all four databases in addition to another 28 articles marked as duplicates manually. An additional 203 articles were excluded following title and abstract screening. 134 full texts were reviewed, of which a total of 7 articles met criteria and were included. The quality of 6 of the 7 articles was assessed using the JBI Critical Appraisal Checklist for Analytical Cross-Sectional Studies (See Appendix Table 1); the quality of 1 study was assessed using the JBI Critical Appraisal Checklist for Cohort Studies (See Appendix Table 2) [17].

Study Characteristics

The review was comprised of a total of 1148 participants across 7 studies, 50.7% of which were male. Central tendency measures of age were not consistent across all studies but most reported either a mean or median age between 30 and 50 years, with only one study [18] investigating a geriatric population.

Out of the seven papers selected for review, four of them studied patients with inflammatory bowel disease (IBD) [14,15,18,19]. Melchior 2017 [20] studied IBS patients, Liskiewicz 2021 [21] studied hospital in-patients with MDD, and Chojnacki 2022 [22] studied both healthy controls and patients suffering from small intestinal bacterial overgrowth (SIBO).

Measures

Out of the studies selected, the scales used to assess depression were the Patient Health Questionnaire (PHQ-9) [14,15,19], the Hamilton Depression Rating Scale (HDRS24/HAM-D) [21,22], the Geriatric Depression Scale (GDS) [18], and the Hospital Anxiety and Depression Scale (HADS-D) [20]. All these scales are validated for assessing depression severity in clinical settings [23–26].

Four of the total included studies tested FC from stool samples as part of the procedure, while two reported using electronic medical records to assess FC concentration [18,19]. Mules, 2022 did not explicitly state their testing method for FC [15].

Association between Depression Scores and FC

Six of the seven included articles investigated the relationship between FC and depression scores through a correlational analysis. Of these, two articles found no significant association between FC concentrations and depression severity [15,20], two found significant moderate positive correlations between FC concentrations and depression severity [14,22], and one found a significant weak positive correlation between the two variables in Crohn's disease (CD) patients but not ulcerative colitis patients (UC) [19]. One study found no correlation between baseline depression scores and FC concentrations but found that the change in depression scores after a six-week escitalopram treatment regimen was correlated with the change in FC concentrations [21]. No other studies investigated FC and depression scores longitudinally. See Appendix Table 3 for *P*-values and additional information about each study.

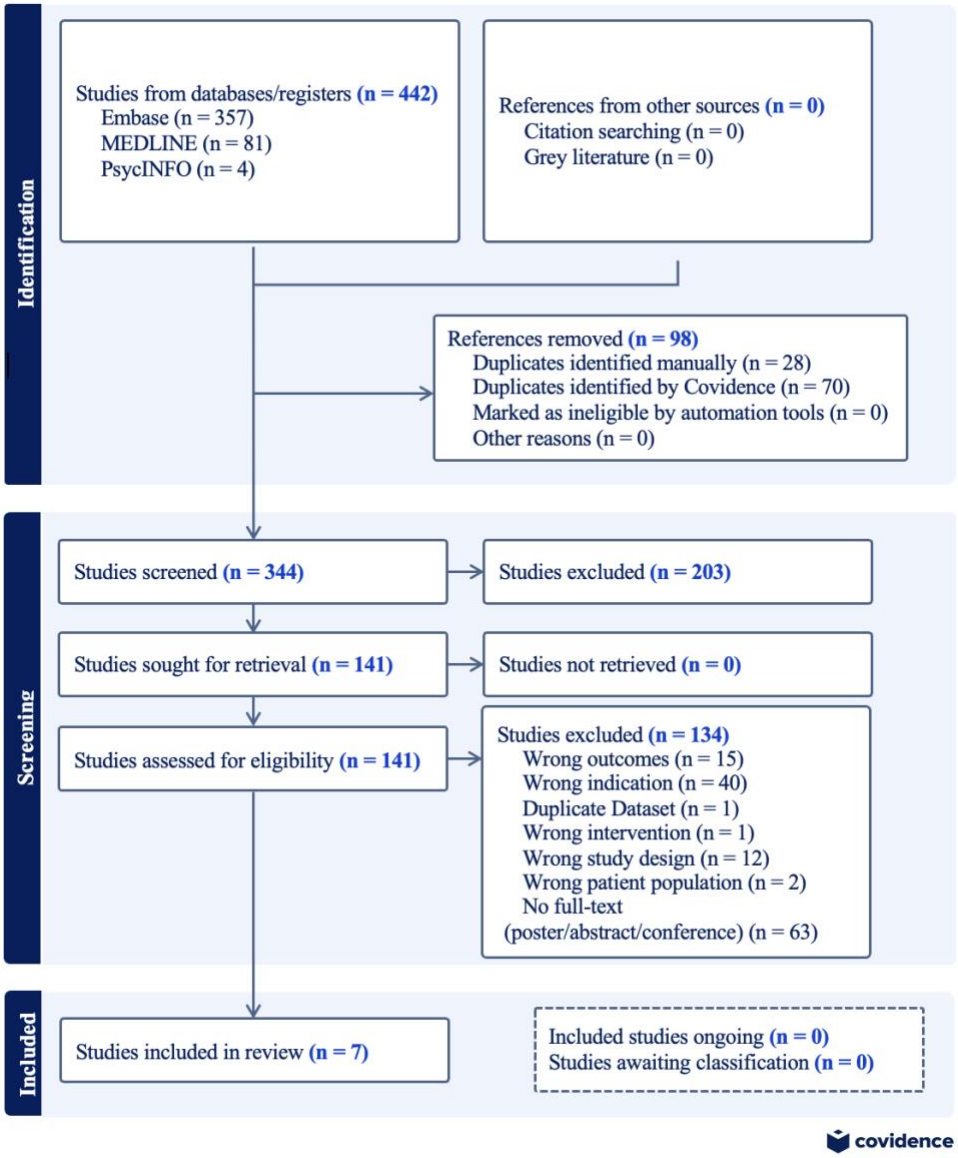

Figure 1. PRISMA flowchart showing identification and selection of studies from databases. Covidence software was used to generate this diagram (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia. Available at www.covidence.org) [16].

Two studies assessed the relationship between FC and depression scores by stratifying participants into low and high FC concentration groups and assessing the difference in depression scores between groups. Asscher et al.— who did not report conducting a direct correlational analysis between FC levels and depression severity— compared participants whose FC concentrations were less than 250 µg/g to those with concentrations greater or equal to 250 µg/g [18]. The difference in proportion of abnormal GDS scores between these groups was non-significant. This non-significant difference was upheld in a sensitivity analysis, where comparisons were between participants whose FC concentrations were less than 50 µg/g vs greater than or equal to 50 µg/g. Geiss et al. [19]— who originally found a weak positive correlation between FC levels with depression severity in CD but not UC patients— conducted an additional analysis separating participants whose FC samples were collected within 30 days of completing the PHQ-9 from those whose samples were collected within 3 days of questionnaire completion. Within these subgroups, Geiss et al. did not conduct a correlational analysis, instead comparing participants whose FC concentrations were less than 200 µg/g to those with FC concentrations greater than or equal to 200 µg/g [19]. Here, the difference in depression scores between the 'high FC' and 'low FC' groups was only significant if the analysis included only CD patients whose FC concentrations were determined within 3 days of completing the depression questionnaire. If all CD patients

whose FC levels were collected within 30 days of questionnaire completion were included, there were no significant differences in depression scores between high and low FC groups. In all analyses — whether including only participants whose FC levels were determined within 3 days of questionnaire completion or any participants whose FC levels were determined within 30 days — the difference in depression scores between groups for UC patients was non-significant. See Appendix Table 3 for *P*-values and additional information about each study.

Attempts were made to assess the impact of collection time of FC in relation to the completion of the depression questionnaire; however, a lack of disclosure in that regard made it impractical to attempt to draw a conclusion.

Discussion

Despite calprotectin's key role in detecting mucosal inflammation [27] and deterioration of the epithelial lining [28], this review did not find any conclusive evidence using FC as a biomarker for depression. While four studies reported a significant association between FC and depression scores, three of the seven included studies did not. Importantly, although the sample size was heterogeneous across the seven studies, this inconclusive result is likely not due to differences in sample size; both non-significant and significant findings alike were found in studies with robust sample sizes (see Appendix Table 3).

More likely, the unclear association between FC and depression could be explained by difference in timing of FC sample collection relative to depression questionnaire administration. Geiss 2018—using a sample of 348 participants (see Appendix Table 3)—reported significant differences in depression severity between high and low FC concentration groups but only in a subgroup of patients whose FC levels were collected within 3 days of depression questionnaire completion [19]. This suggests that the relationship between FC and depression severity is time-dependent; if too much time has passed between the collection of FC samples and measurement of depressive symptoms, they would no longer be related. Accordingly, FC levels may be a poor predictor of future depression severity. This finding would be supported by current knowledge in the literature, suggesting that FC levels are sensitive to short-term changes in the gut-brain-immune axis [29]. However, most included studies did not report the time elapsed between when FC samples were collected and when depression questionnaires were administered, making the time dependency of FC levels' association with depression severity difficult to investigate. It is also possible that any undisclosed differences in timing of FC measurement relative to depression symptom assessment is what contributed to the inconsistency in reported associations between FC and depression severity across studies. Overall, more research is needed to clarify whether FC concentrations are acutely associated with depression scores within a specified time frame.

The association between FC levels and depression severity may also vary between subsets of the population. Geiss et al. noted that there was a significant positive correlation between FC levels and depression severity in CD patients but not in UC patients [19]. This was also observed when only patients whose FC levels were collected within 3 days of PHQ-9 completion were included in analyses (see Appendix Table 3). This suggests that the relationship between FC levels and depression may not be durable across different disease populations. Although Mules et al. [15] also provided separate correlations between FC levels and depression severity for UC and CD groups, the authors found nonsignificant correlations in both populations. However, Mules et al. [15] did not report the time period between the depression assessment and FC sampling, which as discussed [19], may have affected the association between FC levels and depression severity. It is possible that FC levels and depression severity are durably associated in CD but not UC patient populations but that this association was masked by lack of control of time elapsed between FC sample collection and depression questionnaire completion. Unfortunately, no other included studies on IBD populations reported examining the association between FC levels and depression separately for CD and UC populations, making this difficult to ascertain. Further exploration is needed to clarify whether the relationship between FC and depression severity differs between disease populations.

Another important consideration in relating FC to depression is how groups can be stratified by FC concentration. In the study conducted by Asscher et al., the authors did not directly report the relationship between FC concentration and depression severity scores, instead comparing the proportion of abnormal GDS scores between 'high FC' and 'low FC' concentration groups [18]. The high FC group was defined by FC concentration of greater than or equal to 250 µg/g, while the low FC group corresponded to FC concentrations of less than 250 µg/g. Asscher et al. found no difference in the proportion of abnormal GDS scores between their groups (which they confirmed in a sensitivity analysis using ≥ 50µg/g and <50 µg/g to define high and low FC groups respectively) [18]. Iordache and colleagues offered a novel insight, correlating absolute FC concentration with questionnaire scores in order to determine the ideal threshold for detection of clinical depression [14]. Here, Iordache et al. reported that a cut-off of 131 µg/g or higher could potentially be used to predict clinical depression, having a sensitivity of 82%, specificity of 61%, and accuracy of 70% in their sample population [14]. This is a unique finding in of itself, but also could explain the non-significant findings in the study conducted by Asscher et al.—the latter study did not use an optimal cut-off point for FC concentration to detect depression [18]. However, it is also important to note that the differences in sample population— notably age and measures— make it difficult to generalize in this way across the two studies.

Further, neither study reported the timing of FC sample collection relative to depression questionnaire administration which may have been important to the relationship between FC and depression [14,18,30].

An intriguing finding of this review was that *changes* in FC concentration during a depression treatment course were correlated with changes in depression severity. According to the study conducted by Liskiewicz et al. [21], although baseline measures of depression severity and FC concentrations were not significantly associated, the change in HDRS24 scores had a significant strong positive correlation with change in FC concentration over the course of a depression treatment (see Appendix Table 3). Given this finding, there may be utility in using FC to monitor patient progress during a depression treatment program. The study's findings also point to an interesting and novel insight: when FC concentration and depression severity level are correlated at one time point, it's possible that individual differences— such as age, underlying inflammation, and gut health— mask the association between FC and depression. However, when examining longitudinal changes [21], the association can be better teased out from these confounds. This finding could also explain the lack of consensus in the other included studies: if individual variability was controlled for by focusing on the *change* in FC concentration and depression questionnaire score, there is potential for a more robust association. Overall, the study conducted by Liskiewicz et al. supports the association between FC and depression severity in a population without gastrointestinal illness [21]. It is important to note; however, that their sample size was small (n = 16) which limits the generalizability of their findings. Further investigation into whether FC can accurately gauge the change in severity of depression over time is needed.

The small number of studies in the review was a limiting factor, especially given the differences in methodology and sample characteristics across the studies. As discussed, several factors such as the FC collection procedure, age of the sample population, and disease comorbidity can have a significant impact on an individual's FC levels; therefore, the variation in our study made it difficult to provide a conclusive interpretation about the association between FC concentration and depression severity. Majority of the studies included in our analyses had focused on a specific disease population–4 in IBD [14,15,18,19], 1 in IBS [20], and 1 in SIBO [22]. Given the lack of research in healthy populations and other diseased populations, it is uncertain if FC and depression correlations can be applied to other populations [21].

Conclusions

This systematic review did not find a consistent link between FC as a biomarker for depression due to the lack of consistency in the methodology and results of included studies; however, more research is warranted because of the possible implications of FC as a predictor of treatment outcome in depression. Should this be further established, FC may have a role in antidepressant therapies due to its ability to monitor a patient's progress throughout their treatment. The inconclusive findings of this study highlight the need for more extensive research into the field of intestinal biomarkers for depression.

List of Abbreviations Used

CD: Crohn's disease
IBD: inflammatory bowel disease
FC: fecal calprotectin
UC: ulcerative colitis
GI: gastrointestinal
PHQ-9: patient health questionnaire-9
HDRS24/HAM-D: Hamilton depression rating scale – 24 items
GDS: geriatric depression scale
GAD-7: general anxiety disorder scale – 7 items
CRP: C-reactive protein
MDD: major depressive disorder
µg/g: micrograms per gram

Conflicts of Interest

The authors have no conflicts of interests to disclose.

Ethics Approval and/or Participant Consent

This systematic review did not require ethics approval or participant consent due to the study design.

Authors' Contributions

KC: made substantial contributions to the design of the study, the collection of data as well as interpretation and analysis of the data, revised the manuscript critically, and gave approval of the version to be published.
BD: made substantial contributions to the design of the study, the collection of data as well as interpretation and analysis of the data, revised the manuscript critically, and gave approval of the version to be published.

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