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A Systematic Review and Meta-Analysis of Depression and Protein–Energy Wasting in Kidney Disease

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Introduction: Depression comorbid with chronic disease may be mediated by inflammation. We sought to characterize relationships between inflammatory biomarkers and depressive symptoms in patients with chronic kidney disease and end-stage kidney disease.

Methods: A systematic literature search was conducted by 2 authors up to March 19, 2019, for studies of patients with chronic kidney disease or end-stage kidney disease evaluating circulating inflammatory biomarkers associated with depression of chronic disease: albumin, C-reactive protein (CRP), high-sensitivity CRP, interleukin-6 (IL-6), tumor necrosis factor-α, and interleukin-1. Standardized mean differences in biomarkers between individuals with and without depression were computed and analyzed using mixed effects models. Correlations between biomarkers and the severity of depressive symptoms were computed.

Results: Thirty-four studies (5652 participants) compared biomarkers between depressed and nondepressed individuals. Individuals with depression had lower albumin levels (standardized mean difference, −0.37; 95% confidence interval [CI], −0.61 to −0.13), higher CRP levels (standardized mean difference, 0.76; 95% CI, 0.16–1.37), and higher IL-6 levels (standardized mean difference, 0.42; 95% CI, 0.21–0.63). Studies were heterogeneous for albumin, CRP, high-sensitivity CRP, and tumor necrosis factor-α. Twenty-three studies (3047 participants) investigated correlations between biomarkers and depressive symptoms. The severity of depressive symptoms correlated with albumin ($Z = -0.25$; 95% CI, −0.36 to −0.14), high-sensitivity CRP ($Z = 0.28$; 95% CI, 0.13–0.43), and IL-6 ($Z = 0.34$; 95% CI, 0.18–0.49). There was heterogeneity across studies of IL-6. Only 6 studies (321 participants) investigated the effect of antidepressant treatment on inflammatory biomarkers, which was insufficient to combine in meta-analysis.

Conclusion: Lower albumin and higher IL-6 were associated with both the presence and severity of depression, CRP with the presence of depression, and high-sensitivity CRP with the severity of depressive symptoms. The effect of interventions to lower inflammation in patients with kidney disease and depression deserves investigation.

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Major depressive disorder is prevalent in up to 25% of individuals with chronic kidney disease (CKD) and end-stage kidney disease (ESKD) compared with ∼7% in the general population and is associated with death, hospitalization, and dialysis initiation.[1–4] In the general population, circulating inflammatory biomarkers, such as interleukin-6 (IL-6), high-sensitivity C-reactive protein (hsCRP), and tumor necrosis factor-α (TNF-α), are associated with the presence of depressive symptoms,[5–7] and biomarkers of chronic inflammation predict incident depression.[8] Associations between depression, elevated inflammatory cytokine levels, protein catabolism, and cardiovascular disease have led to the proposal of protein–energy wasting syndrome as a potential mechanism underlying

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the high comorbidity of depression with chronic medical illnesses, poor response to antidepressant medications in patients with chronic disease, and associations of depression with long-term morbidity and mortality.[9–13] *Protein–energy wasting* refers to the complex constellation of factors including inflammation, malnutrition, comorbid medical illnesses, protein catabolism, metabolic acidosis, hormonal abnormalities, and loss of kidney function that contribute to cardiovascular disease and muscle wasting in patients with CKD and ESKD.[14,15] Given that CKD and ESKD are disease states associated with increased underlying systemic inflammation and protein–energy wasting[13,16,17] and that depression is prevalent and associated with adverse outcomes in these patient populations, the association of inflammation with depressive symptoms in such patients deserves exploration.

Several observational studies have sought to investigate these associations in patients with dialysis-dependent ESKD, and data are scarcer in those with nondialysis CKD. These studies reported heterogeneous results, likely because many were limited by small sample sizes, which do not allow the derivation of definitive conclusions. The objective was to, therefore, conduct a systematic review and meta-analysis of observational studies that investigated (i) associations of circulating inflammatory biomarkers and common measures of malnutrition with depression prevalence in patients with CKD and ESKD; (ii) associations of these circulating protein–energy wasting biomarkers with depressive symptom severity, as captured by self-report measures of depressive affect; and (iii) the effect of treatment with antidepressant medications on change from baseline in the levels of these biomarkers. The rationale was to summarize relationships between inflammatory biomarkers and depression to provide a resource for future investigation to identify novel depression prediction models and treatment strategies in patients with CKD and ESKD.

METHODS

Search Strategy and Study Selection Criteria

We performed a systemic review and meta-analysis in accordance with published guidelines outlined by the Preferred Reporting Items for Systemic Reviews and Meta-Analyses.[18] A systemic search was conducted in PubMed for published studies up to March 19, 2019, for the keyword search terms "depression," "hemodialysis," "peritoneal dialysis," "chronic kidney disease," "end-stage renal disease," "cytokine," "inflammation," "syndrome," "complex," and "interleukin." The search was limited to human studies. Only studies in the English language were included. Studies involving recipients of kidney transplantation were excluded. Two authors (GM and DL) independently evaluated all resulting search citations by title and abstract and the full text of any reference that seemed pertinent to the questions of interest. Discrepancies were resolved by a third author (LPG). We included studies of prespecified circulating inflammatory biomarkers previously reported to be associated with depression of chronic disease: albumin, C-reactive protein (CRP) measured by the regular or high-sensitivity assay, IL-6, TNF-α, and interleukin-1 (IL-1).[19,20] Studies included in the analysis involved patients with CKD and/or ESKD and addressed at least 1 of the 3 following areas: (i) comparison of circulating inflammatory biomarker levels between individuals with and without depression, (ii) correlation of circulating inflammatory biomarker levels with severity of depressive symptoms, or (iii) change in inflammatory biomarkers from baseline after treatment with an antidepressant medication. We included all study designs, including retrospective studies, cross-sectional studies, prospective cohort studies, and clinical trials.

Data Extraction and Classification

Two authors (GM and LPG) independently extracted data from all selected studies and individually recorded the data into the meta-analysis electronic database sequentially. Specific data extracted were number of participants, presence of nondialysis CKD or ESKD, type of dialysis therapy (hemodialysis [HD] vs. peritoneal dialysis [PD]), measurement tool and definition or cutoff used for depression diagnosis, and type and level of circulating inflammatory biomarker. Two authors (GM and LPG) independently evaluated factors such as the study design and the risk of selection or publication bias. Any differences between the 2 reviews were resolved through consensus.

Outcome Measures

The prespecified primary outcome was the association of inflammatory biomarkers with the presence of depression, as defined in each study included in the meta-analysis. Secondary outcomes included correlations of inflammatory biomarkers with the severity of depressive symptoms as ascertained by self-report measures and the impact of treatment with antidepressant medications on change from baseline in biomarkers levels.

Statistical Analysis

Meta-analysis was performed using a mixed effects model with study as the random effect and implemented in the "metaphor" package in R.[21] Thus, we assumed that the studies included in this analysis were

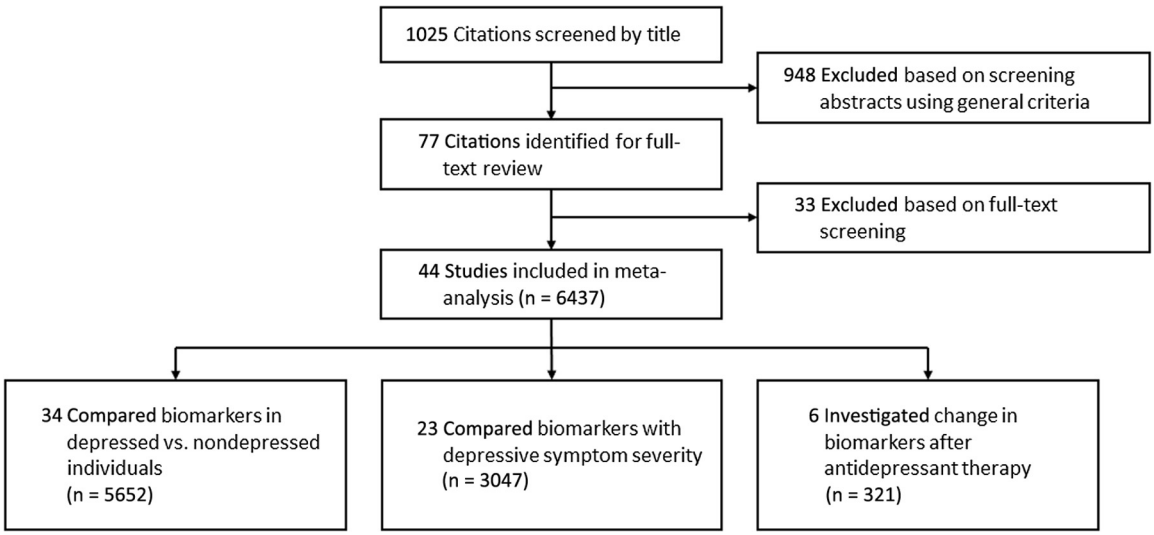

Figure 1. Identification of eligible studies.

a random sample from a larger population of studies. The Knapp and Hartung adjustment (appropriate for the meta-analysis involving a small number of studies) accounted for the fact that the true effect heterogeneity parameter (τ^2) was estimated rather than known.[22] Heterogeneity was measured by the I^2 statistic, where values between 75% and 100% indicated considerable heterogeneity, and the Q statistic was tested for significant heterogeneity across studies.[23] Heterogeneity was investigated with regard to 2 factors with sufficient numbers of studies for analysis: sample composition (HD vs. other) and depression outcome measure (Beck Depression Inventory [BDI] vs. other). No systematic bias was observed because of stratification or adjustment for these factors. Funnel plot asymmetry was tested with a rank correlation test to ascertain potential publication bias.[24] The quality of each study was measured using Grading of Recommendations Assessment, Development, and Evaluation criteria.[25] Meta-analysis was performed for standardized mean differences between depressed and nondepressed participants and for Fisher *r*-to-*Z* transformed correlations between biomarkers and the severity of depressive symptoms for each inflammatory biomarker for each study that provided the appropriate outcome measure. Fisher *r*-to-*Z* transformation was used because it provides stable variance estimates and a more normal distribution. Studies providing a linear regression β coefficient rather than a correlation coefficient were not included in the meta-analysis of correlations. In a sensitivity analysis, a meta-analysis of correlations was performed without application of Fisher *r*-to-*Z* transformation. In a prespecified analysis plan, we required that only biomarkers with a minimum of ≥4 studies reporting the necessary statistics would be included in the meta-analysis. Although meta-analysis can be performed with only 2 studies, we believe that 2 studies would not be adequate to obtain useful estimates. In contrast, requiring a large number of studies would limit the number of biomarkers that could be analyzed. Therefore, we chose a minimum of 4 studies in an attempt to balance statistical considerations with analysis of as many biomarkers as possible.

RESULTS

Study Flow and Characteristics

Our search criteria revealed 1025 citations. A total of 948 were excluded by screening or detailed review criteria. Forty-four studies, including 6437 unique participants, met criteria for inclusion (Figure 1). The majority of included studies were conducted in patients with ESKD. Of these, 26 sampled only patients on HD, 5 sampled only patients on PD, and 11 sampled both patients on HD and those on PD. Only 5 studies included participants with nondialysis CKD, and 2 were conducted exclusively in patients with nondialysis CKD. Studies were heterogeneous; several different scales were used to measure depressive symptoms; and inconsistent cutoffs of these scales were used to identify the presence of depression. Because of the observational nature of the majority of the data, most studies were classified as moderate or low according to Grading of Recommendations Assessment, Development, and Evaluation criteria (Tables 1 and 2).[25–64]

Inflammation and the Presence of Depression

In CKD and ESKD samples, of the 44 studies included, 34 tested whether levels of inflammatory biomarkers differed between individuals with and without depression (Table 1). Serum albumin was the most frequently studied biomarker, tested in 30 studies.

Table 1. Comparisons of inflammatory biomarkers in CKD or ESKD samples with vs. without depression

Study	Study design	GRADE score	Sample	No. of patients with depression	Depression definition (categorically)	Biomarkers measured
Dogan *et al.*[26]	Cross-sectional	Low	43 HD	21	HAMD >7	Albumin, CRP
Kalender *et al.*[27]	Cross-sectional	Low	68 HD, 47 PD, 26 CKD	34	*DSM IV* criteria	Albumin, CRP
Micozkadioglu *et al.*[28]	Cross-sectional	Low	110 HD	71	CDI >10	Albumin, CRP
Boulware *et al.*[29]	Prospective cohort	Moderate	688 HD, 229 PD	221	MHI-5 ≤52	Albumin, CRP, IL-6
Kalender *et al.*[30]	Cross-sectional	Low	42 PD	11	SCID-I	hsCRP, IL-6, TNF-α, IL-1
Simic Ogrizovic *et al.*[9]	Prospective cohort	Low	77 HD, 51 PD	58	BDI ≥14	Albumin
Hsu *et al.*[31]	Cross-sectional	Low	51 HD	18	HADS ≥8	Albumin, CRP
Montinaro *et al.*[32]	Cross-sectional	Very low	30 HD	19	HADS ≥8	Albumin
Bossola *et al.*[33]	Cross-sectional	Low	80 HD	42	BDI ≥15	Albumin, hsCRP, IL-6
Ko *et al.*[34]	Cross-sectional	Low	81 PD	43	BDI >15	Albumin, hsCRP, TNF-α
Gyamlani *et al.*[35]	Cross-sectional	Low	71 CKD	18	CES-D ≥16	Albumin, CRP
Li *et al.*[36]	Cross-sectional	Moderate	142 PD	37	HAMD ≥10	Albumin, CRP
Hung *et al.*[37]	Cross-sectional	Moderate	146 HD	68	BDI ≥14	Albumin, hsCRP, IL-6
Chilcot *et al.*[38]	Prospective cohort	Low	132 HD, 28 PD	41	BDI ≥16	Albumin
Bornivelli *et al.*[39]	Cross-sectional	Low	45 HD	16	HAMD >7	Albumin, CRP
Armaly *et al.*[40]	Cross-sectional	Low	71 HD	31	BDI >11 or HADS >18	Albumin, CRP
Kim *et al.*[41]	Cross-sectional	Low	78 HD	35	BDI ≥20	Albumin
Cilan *et al.*[42]	Prospective cohort	Low	40 HD	9	*DSM IV* criteria	IL-6, TNF-α, IL-1
Wang *et al.*[43]	Cross-sectional	Moderate	195 HD	47	MINI	Albumin, CRP, IL-6, TNF-α, IL-1
Taraz *et al.*[44]	Cross-sectional	Moderate	83 HD	51	BDI ≥16	Albumin, hsCRP, IL-6, TNF-α, IL-1
Su *et al.*[45]	Cross-sectional	Low	274 HD	118	BDI ≥14	Albumin, hsCRP
Cilan *et al.*[46]	Prospective cohort	Low	40 PD	10	*DSM IV* criteria	Albumin
Preljevic *et al.*[47]	Cross-sectional	Low	84 HD, 25 PD	24	SCID-I	Albumin
Nowak *et al.*[48]	Cross-sectional	Low	694 HD	268	BDI >16	CRP
Knuth *et al.*[49]	Cross-sectional	Low	75 HD	36	BDI ≥14	Albumin, IL-6
Fan *et al.*[50]	Prospective cohort	Moderate	323 HD	83	CES-D ≥16	Albumin
Loosman *et al.*[51]	Prospective cohort	Low	100 CKD	34	BDI ≥11	Albumin
Bossola *et al.*[52]	Cross-sectional	Moderate	100 HD	74	BDI ≥10	Albumin, hsCRP, IL-6
Ekramzadeh *et al.*[53]	Cross-sectional	Low	110 HD	80	BDI ≥10	Albumin
Gok Oguz *et al.*[54]	Cross-sectional	Low	40 PD	16	BDI ≥10	Albumin
Barros *et al.*[55]	Prospective cohort	Low	104 HD	32	BDI ≥15	Albumin
Haverkamp *et al.*[56]	Prospective cohort	Moderate	436 HD, 54 PD	211	BDI ≥13	TNF-α
Jong *et al.*[57]	Cross-sectional	Low	129 HD	43	BDI ≥14	Albumin, hsCRP, IL-6, TNF-α
Chilcot *et al.*[58]	Cross-sectional	Low	396 HD	121	BDI ≥16	Albumin

BDI, Beck Depression Index; CDI, Cognitive Depression Index; CES-D, Center for Epidemiologic Studies-Depression; CKD, chronic kidney disease; CRP, C-reactive protein; *DSM IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*; ESKD, end-stage kidney disease; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; HADS, Hospital Anxiety and Depression Scale; HAMD, Hamilton Depression Scale; HD, hemodialysis; hsCRP, high-sensitivity C-reactive protein; IL, interleukin; MHI-5, Medical Outcomes Study Short Form-36; MINI, Mini International Neuropsychiatric Interview; PD, peritoneal dialysis; SCID-I, Structured Clinical Interview for DSM-IV Axis I Disorders; TNF-α, tumor necrosis factor-α.

Overall, serum albumin level was found to be lower in depressed than in nondepressed individuals (standardized mean difference, −0.37; 95% confidence interval [CI], −0.61 to −0.13) (Figure 2a[9,26–58]). CRP reached statistical significance in the meta-analysis (standardized mean difference, 0.76; 95% CI, 0.16–1.37), but hsCRP did not (Figure 2b and c). IL-6 level was higher in depressed than in nondepressed individuals (standardized mean difference, 0.42; 95% CI, 0.21–0.63) (Figure 2d). The few studies of TNF-α (n = 7) and IL-1 (n = 4) showed no association of levels of these biomarkers with the presence of depression (Figure 2e and f). Studies of each biomarker except IL-1 were significantly heterogeneous ($P < 0.001$), with I^2 statistic >75% for all biomarkers except IL-1 ($I^2 = 0\%$) and IL-6 ($I^2 = 64\%$), but all tests of funnel plot asymmetry were nonsignificant (Figure 2a–f; Supplementary Figure S1). The underlying data used to compare biomarkers in those with versus without depression are presented in Supplementary Table S1.

Inflammation and the Severity of Depressive Symptoms

A total of 23 studies reported cross-sectional correlations of inflammatory biomarkers with the severity of depressive symptoms in patients with CKD and ESKD (Table 2). By Fisher *r*-to-*Z* transformation, the serum albumin level negatively correlated with the severity of depressive symptoms ($Z = -0.25$; 95% CI, −0.36 to −0.14) (Figure 3a[9,13,26,27,33,34,36–39,41,43,44,48,49,53,57,59–64]). CRP and hsCRP levels correlated positively with the severity of depression in several individual studies. In meta-analysis, CRP did not reach statistical significance (Figure 3b) but hsCRP levels correlated significantly

Table 2. Correlations of the severity of depressive symptoms with inflammatory biomarkers in patients with CKD and ESKD

Study	Study design	GRADE score	Sample	Depressive symptom measure (continuous score)	Biomarkers measured
Dogan *et al.*[26]	Cross-sectional	Low	43 HD	HAMD	Albumin, CRP
Kalender *et al.*[27]	Cross-sectional	Low	68 HD, 47 PD, 26 CKD	BDI	Albumin, CRP
Kalender *et al.*[59]	Cross-sectional	Low	68 HD, 47 PD, 26 CKD, 66 controls	SF-36 mental composite	Albumin, CRP
Dervisoglu *et al.*[60]	Cross-sectional	Low	31 HD, 31 PD, 31 CKD	BDI	IL-6, TNF-α
Simic Ogrizovic *et al.*[9]	Prospective cohort	Low	77 HD, 51 PD	BDI	Albumin, hsCRP, IL-6
Bossola *et al.*[33]	Cross-sectional	Low	80 HD	BDI	Albumin, hsCRP, IL-6
Ko *et al.*[34]	Cross-sectional	Low	81 PD	BDI	Albumin, hsCRP, TNF-α
Sonikian *et al.*[61]	Cross-sectional	Low	27 HD, 17 PD	Zung Self-Rating Depressoin Scale	IL-6
Chilcot *et al.*[38]	Prospective cohort	Low	132 HD, 28 PD	BDI	Albumin, CRP
Hung *et al.*[37]	Cross-sectional	Moderate	146 HD	BDI	Albumin, hsCRP, IL-6
Li *et al.*[36]	Cross-sectional	Moderate	142 PD	HAMD	Albumin, CRP
Choi *et al.*[13]	Prospective cohort	Low	81 HD	BDI	Albumin, hsCRP
Kim *et al.*[41]	Cross-sectional	Low	78 HD	BDI	Albumin, hsCRP
Taraz *et al.*[44]	Cross-sectional	Moderate	83 HD	BDI	Albumin, hsCRP, IL-6, TNF-α, IL-1
Bornivelli *et al.*[39]	Cross-sectional	Low	45 HD	HAMD	CRP
Wang *et al.*[43]	Cross-sectional	Moderate	195 HD	HADS + SF-36 depression	Albumin, CRP, IL-6, TNF-α, IL-1
Nowak *et al.*[48]	Cross-sectional	Low	694 HD	BDI	CRP
Knuth *et al.*[49]	Cross-sectional	Low	75 HD	BDI	IL-6
Ekramzadeh *et al.*[53]	Cross-sectional	Low	110 HD	BDI	Albumin
Uglesic *et al.*[62]	Cross-sectional	Low	52 HD, 36 PD	BDI	Albumin, CRP, IL-6
Jong *et al.*[57]	Cross-sectional	Low	129 HD	BDI	Albumin, hsCRP, IL-6, TNF-α
Zhao *et al.*[63]	Randomized trial	High	189 HD	BDI	IL-6
Schricker *et al.*[64]	Cross-sectional	Low	26 HD, 13 PD	Allgemeine Depressionsskala	CRP, IL-6

BDI, Beck Depression Index; CKD, chronic kidney disease; CRP, C-reactive protein; ESKD, end-stage kidney disease; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; HADS, Hospital Anxiety and Depression Scale; HAMD, Hamilton Depression Scale; HD, hemodialysis; hsCRP, high-sensitivity C-reactive protein; IL, interleukin; PD, peritoneal dialysis; SF-36, Short-Form Health-Related Quality of Life 36-item questionnaire; TNF-α, tumor necrosis factor-α.

with the severity of depressive symptoms ($Z = 0.28$; 95% CI, 0.13–0.43) (Figure 3c). IL-6 levels also associated with the severity of depressive symptoms in the majority of studies and in pooled analysis ($Z = 0.34$; 95% CI, 0.18–0.49) (Figure 3d). TNF-α level, investigated in 5 studies, was not associated with the severity of depressive symptoms (Figure 3e). Only 2 studies investigated correlations of IL-1 levels with the severity of depressive symptoms, so these were not combined in meta-analysis. Studies were significantly heterogeneous for each biomarker, with studies showing considerable heterogeneity except for TNF-α ($I^2 = 74\%$) and hsCRP ($I^2 = 70\%$), but tests of funnel plot asymmetry were nonsignificant (Figure 3a–e; Supplementary Figure S2). The results were similar using nontransformed correlation coefficients (Supplementary Figure S3A–E). The underlying data used to evaluate correlations of depressive symptoms with inflammatory biomarkers are presented in Supplementary Table S2.

Effect of Antidepressant Treatment on Inflammatory Biomarkers

Only 6 studies, all in ESKD samples, investigated whether treatment with antidepressant medications affected systemic levels of inflammatory biomarkers (Table 3).[65–67] Selective serotonin reuptake inhibitors (SSRIs) were used for depression treatment in all the studies. Serum albumin level, measured in 3 studies, was not shown to change with antidepressant therapy.[46,66,67] CRP level was found to decrease with sertraline treatment in 1 study,[67] but 3 others, 2 of which used the high-sensitivity assay, found no difference.[46,65,66] The most commonly studied biomarker was IL-6, which was included in 5 studies. Of these, 2 showed no difference in IL-6 levels,[42,63] 2 showed that IL-6 level increased in those whose depressive symptoms responded to treatment,[46,65] and 1 showed that IL-6 level significantly decreased with sertraline treatment.[66] Three of the 4 studies of TNF-α showed no difference after treatment with sertraline or fluoxetine,[42,46,65] but the largest study showed that TNF-α level decreased after 12 weeks of sertraline treatment.[66] Two of the 3 studies that reported IL-1 showed a significant change, but in one the level decreased and in the other it increased.[46,65]

DISCUSSION

We report the following findings in patients with CKD and ESKD: (i) the presence of depression, albeit ascertained by variable scales and definitions, was associated with lower serum albumin and higher plasma CRP and IL-6 levels; (ii) more severe depressive symptoms

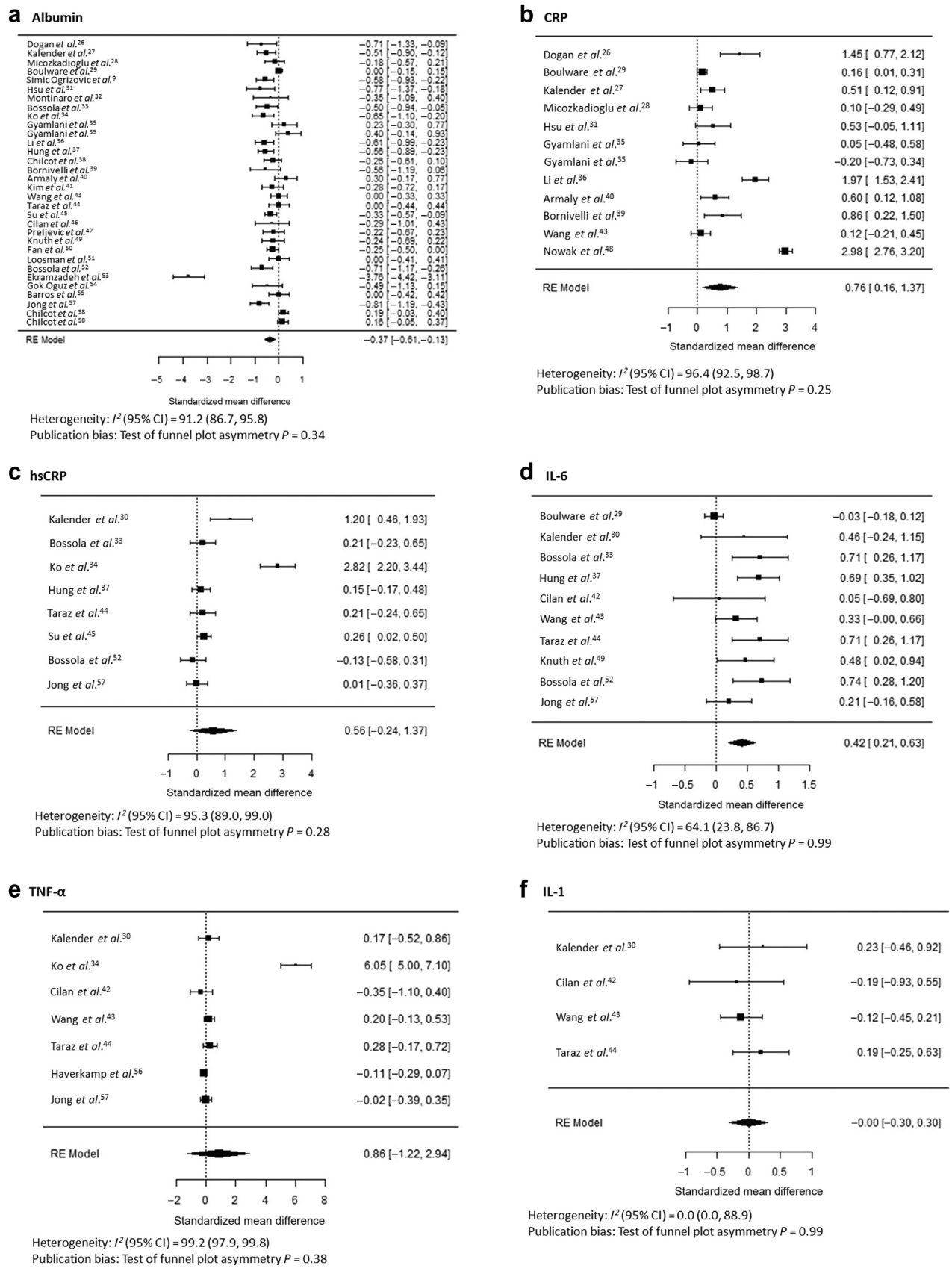

Figure 2. Standardized mean differences between individuals with and without depression, as defined in each study, in albumin (a), C-reactive protein (CRP) (b), high-sensitivity CRP (hsCRP) (c), interleukin-6 (IL-6) (d), tumor necrosis factor-α (TNF-α) (e), and interleukin-1 (IL-1) (f) levels.[9,26–58] RE, random effects.

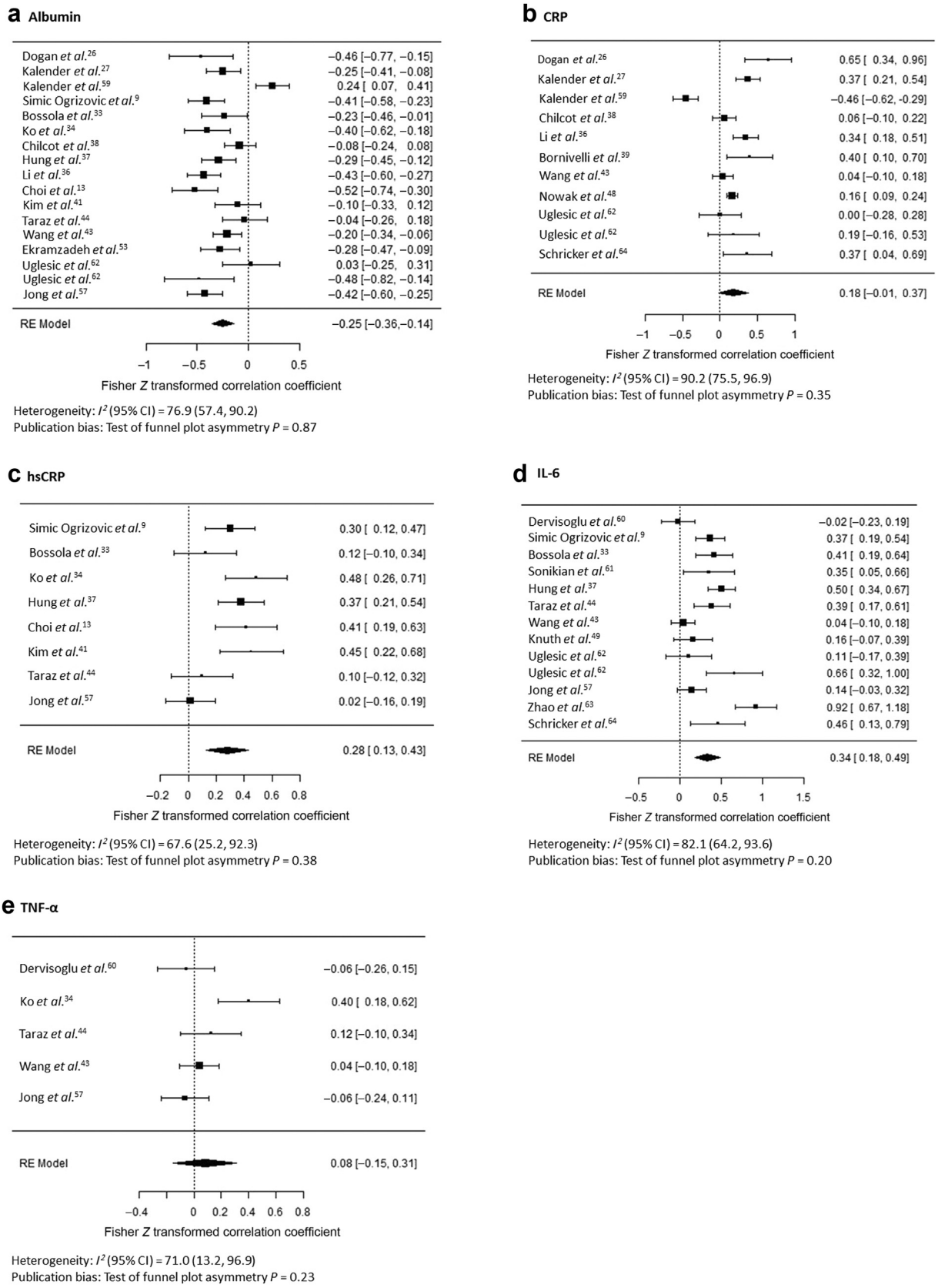

Figure 3. Correlations of depressive symptoms, taken continuously, with albumin (a), C-reactive protein (CRP) (b), high-sensitivity CRP (hsCRP) (c), interleukin-6 (IL-6) (d), and tumor necrosis factor-α (TNF-α) (e) levels.[9,13,26,27,33,34,36–39,41,43,44,48,49,53,57,59–64] RE, random effects.

Table 3. Clinical trials of change in inflammatory biomarker levels with treatment of depression in patients with ESKD

Study	Sample	Intervention	Depression definition	Timing	Albumin level[a] (g/dl)	CRP level[a] (mg/dl)	hsCRP level[a] (mg/dl)	IL-6 level[a] (pg/ml)	TNF-α level[a] (pg/ml)	IL-1 level[a] (pg/ml)
Lee *et al.*[65]	28 HD	Fluoxetine 20 mg/d (8 wk)	BDI ≥11 and HAMD ≥7	Baseline Study exit		219 ± 50[b] 234 ± 60[b]		7.26 ± 2.51 10.58 ± 2.37[c]	80.67 ± 11.4 65.37 ± 5.97	18.87 ± 2.1 10.52 ± 1.18[c]
Cilan *et al.*[42]	9 HD	Sertraline 50 mg/d (8 wk)	*DSM IV* criteria	Baseline Study exit				143.78 ± 85.84 54.63 ± 83.71	109.22 ± 260.15 56.56 ± 162.61	135.89 ± 171.46 127.11 ± 216.27
Cilan *et al.*[46]	10 PD	Sertraline 50 mg/d (8 wk)	*DSM IV* criteria	Baseline Study exit	3.40 ± 0.60 3.21 ± 0.44		9.01 (3.17–57.9) 6.48 (3.17–41.4)	46.5 (5–200) 200 (160–200)[c]	25.5 (1–800) 220 (1–800)	25 (3–340) 375 (3–500)[c]
Taraz *et al.*[66]	50 HD (n = 21 in the sertraline group)	Sertraline 100 mg/d vs. placebo (12 wk)	BDI ≥16	Baseline Study exit	4.3 ± 0.3 4.4 ± 0.3		4.0 (IQR, 2.8) 3.9 (IQR, 3.0)	7.8 (IQR, 6.6) 4.7 (IQR, 4.9)[c]	13 (IQR, 8.9) 8.5 (IQR, 6)[c]	
Zahed *et al.*[67]	35 HD with CRP level >5 mg/dl	Sertraline 50–200 mg/d (12 wk)	BDI >14	Baseline Study exit	3.09 ± 0.86 4.17 ± 0.57	33.5 ± 24.2 15.4 ± 12.6[c]				
Zhao *et al.*[63]	189 HD (n = 63 in the escitalopram group)	Escitalopram 20 mg/d and/or exercise (18 wk)	BDI ≥14					Values not reported; $P > 0.05$ for comparison of baseline to study exit		

BDI, Beck Depression Index; CRP, C-reactive protein; *DSM IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*; ESKD, end-stage kidney disease; HAMD, Hamilton Depression Scale; HD, hemodialysis; hsCRP, high-sensitivity C-reactive protein; IL, interleukin; IQR, interquartile range; PD, peritoneal dialysis; TNF-α, tumor necrosis factor-α.
[a]Presented as mean ± SD or median (IQR) at baseline (before antidepressant treatment) and at study exit.
[b]Reported as 2.19 ± 0.5 mg/ml at baseline and 2.34 ± 0.6 mg/ml at study exit. Values have been converted to mg/dl for consistency in this table.
[c]$P < 0.05$ compared to the baseline value.

correlated with lower albumin and higher IL-6 and hsCRP levels; and (iii) there were insufficient data to determine whether treatment with SSRI antidepressant medications was associated with changes in inflammatory biomarkers from baseline.

Serum albumin is a major biomarker of protein–energy wasting in patients with CKD and ESKD. The levels decrease in states of acute inflammation owing to increased protein catabolism or altered hepatic protein synthesis, and in CKD, it can also be lost in the urine in the setting of nephrotic range proteinuria.[68] In addition, hypoalbuminemia is considered a highly sensitive but nonspecific biomarker of malnutrition[68] and the contribution of malnutrition to protein–energy wasting may explain the association of low circulating albumin level with death in patients with ESKD.[69–72] We showed that serum albumin level was lower in depressed than in nondepressed patients with CKD and ESKD and negatively correlated with the severity of depressive symptoms. The heterogeneous results of these studies likely in part reflect small sample sizes, as larger studies more often detected a difference that smaller studies may have been underpowered to demonstrate. Thus, hypoalbuminemia and protein–energy wasting may in part explain the connection between depression and poor outcomes in patients with CKD and ESKD.[3,13] It is unclear from these data whether the association of decreased albumin with worse depressive symptoms is due to effects of depression on appetite and weight, whether protein–energy wasting augments depressive symptoms, or whether hypoalbuminemia, associated with worse overall poor health in patients with kidney disease, may be reflected in physical and emotional symptoms.

The observed associations of plasma CRP and hsCRP with depression and depressive symptoms proved to be less parsimonious. Both the traditional and high-sensitivity assays for this biomarker had point estimates supporting higher levels in those with depression. This was particularly true of the traditional assay, with a standardized mean difference of 0.76 (95% CI, 0.16–1.37) and a *Z*-transformed correlation coefficient of 0.18 (95% CI, −0.01 to 0.37). Given the association of CRP with the presence of depression and that of hsCRP with the severity of depressive symptoms, overall these data suggest that there likely is an association between depression and systemic inflammation, but this analysis may have been limited by power to detect this association using only the high-sensitivity or traditional assay or by the heterogeneous definitions of depression in the included studies.

The mixed associations of CRP and hsCRP with depression did not clearly vary by study sample size, such that some small studies showed a highly

significant difference[30,34] and some large studies showed none.[37,43] The differences in results were most likely driven by the heterogeneity of depression scales used to ascertain the presence of depression diagnosis or depressive affect or the way depression was defined in the study. Although no studies using cutoffs of the BDI found a difference in CRP levels, 2 found a difference in hsCRP levels.[34,45] In correlation analyses of CRP, almost all the nonsignificant results were seen in comparison with the BDI score, whereas correlations with other measures such as the Hamilton Depression Scale score were found to be significant, even in smaller studies.[26,36,39,64] Consequently, in addition to the previously discussed limitations of these studies, depressive symptoms measured by the BDI may reflect different qualities than did other depression scales, which may have influenced these results.

Higher IL-6 level was strongly associated with both the presence of depression and the severity of depressive symptoms. The smallest studies did not show a difference in IL-6 levels between depressed and nondepressed participants, which may have been limited by sample size.[30,42] Larger studies tended to show higher IL-6 level associated with depression,[33,37,43] but the largest study showed no association.[29] Mean IL-6 levels were similar in both the negative and positive studies, suggesting the possibility of a moderating effect. Protein–energy wasting may explain the variability of these results; studies that showed no relationship between the BDI and IL-6 level reported lower hemoglobin level, lower albumin level, and generally lower body mass index, which could indicate that the severity of protein–energy wasting obfuscates the relationship between IL-6 and the BDI. Most of the studies using the BDI to define depression detected a difference in IL-6 level, whereas studies using other metrics failed to detect a difference, suggesting that the questions on the BDI may more accurately elicit symptom burden exemplified by IL-6–mediated pathways. Many depression scales incorporate questions about both mental and physical symptoms, and it remains unclear whether IL-6 level associates more strongly with physical symptoms such as fatigue than with emotional qualities such as anhedonia. Another possibility is that dialysis modality affects this association; the studies that showed a difference were all conducted exclusively in patients on HD, whereas 2 that showed no difference were conducted in patients on PD or a combination of patients on PD and those on HD.[29,30]

A few studies measured TNF-α or IL-1 levels, and most of these were small, with few participants with depression. Only 1 study that measured TNF-α levels identified a difference associated with depression and a correlation with severity of depressive symptoms,[34] and none of the 4 studies that measured IL-1 levels detected a difference between depressed and nondepressed individuals.[30,42–44] Ultimately there were too few data to determine whether associations between these inflammatory biomarkers and depressive symptoms exist in patients with CKD and ESKD.

Similarly, too few studies have investigated the effect of antidepressant medication therapy on inflammatory biomarkers in CKD or ESKD samples to draw definitive conclusions. Most studies were small, with only 1 including >50 participants.[63] The 2 smallest studies, with 9 and 10 participants, were the only to diagnose depression by *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria,[42,46] while the rest used variable cutoffs of the BDI or the Hamilton Depression Scale. Four studies administered low doses of SSRIs (fluoxetine 20 mg/d or sertraline 50–100 mg/d), despite that no dose adjustments are recommended in patients with CKD or dialysis-dependent patients,[73] leaving questions about whether an adequate dose was trialed. Most of the studies had no control arm to compare against SSRI therapy to determine whether SSRIs accounted for the changes in inflammatory biomarkers or whether some change occurred as part of the natural history of the major depressive episode. Some studies treated participants for only 8 weeks,[42,46,65] so may have missed a time-dependent effect of treatment on inflammation. Interestingly however, the largest study, which also offered the longest treatment course of 18 weeks, showed no difference in IL-6 levels, but unfortunately did not report levels of albumin, CRP, hsCRP, or TNF-α.[63] The limitations of these studies may account for the variability seen in the results, and it remains promising yet unclear whether treatment of depression affects inflammatory biomarkers and whether this correlates with improvement in depressive symptoms in response to treatment. More studies are needed to determine whether existing traditional therapies to treat depressive symptoms may improve systemic inflammation and its association with poor long-term outcomes in patients with CKD and ESKD.

Our analysis has several important limitations. Studies of depression and inflammatory biomarkers were limited by small sample size, variable instruments and thresholds to define depression, and inadequate dosing or treatment duration of antidepressant medications. The heterogeneity, low to moderate quality according to Grading of Recommendations Assessment, Development, and Evaluation criteria, and limitations of the included studies must be considered when interpreting the meta-analysis results. Variability in inclusion and exclusion criteria, sampling methods, or

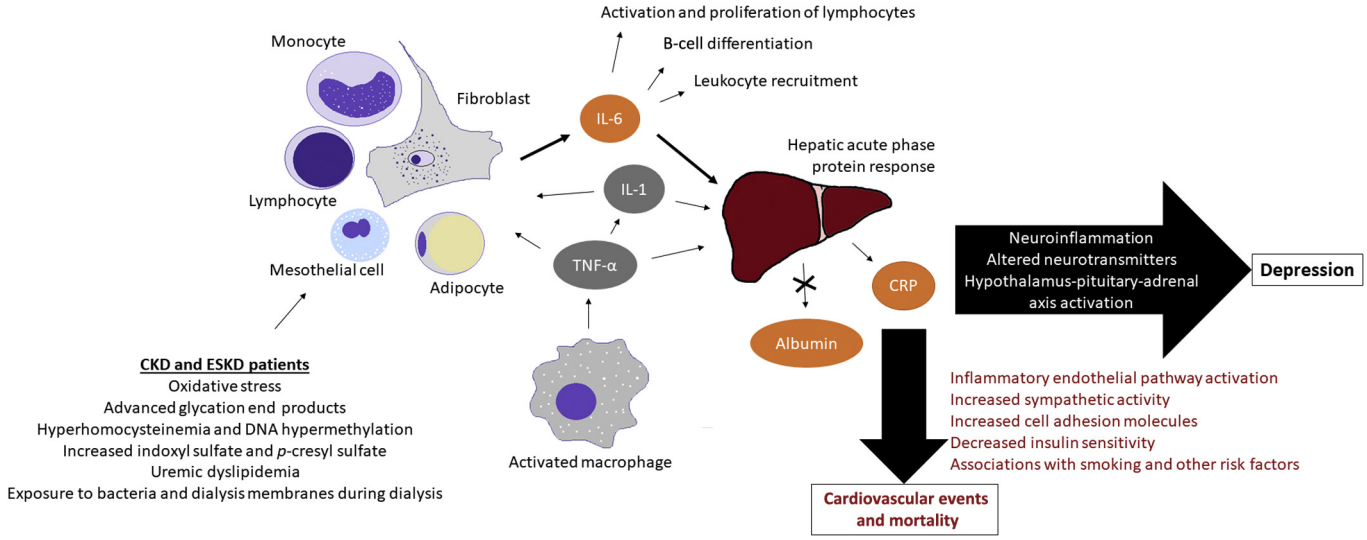

Figure 4. Summary of proposed roles of inflammatory mediators of depression in patients with chronic kidney disease (CKD) and end-stage kidney disease (ESKD) in protein–energy wasting. Orange inflammatory biomarkers are those shown to associate with depression and depressive symptoms, while gray indicates factors that were not shown to associate significantly with depression or depressive symptoms. Clearance of inflammatory cytokines may be decreased in patients with CKD and ESKD, contributing to elevated circulating levels. Furthermore, in patients with CKD and ESKD, oxidative stress, bacterial endotoxins, glycation end products, hyperhomocysteinemia, DNA hypermethylation, uremic toxins, and uremic dyslipidemia can stimulate various pro-inflammatory pathways, particularly leading to the generation of interleukin-6 (IL-6). In addition, primarily activated macrophages produce tumor necrosis factor-α (TNF-α), which has multiple downstream effects, including stimulation of interleukin-1 (IL-1) production and regulating much of the cytokine cascade. TNF-α and IL-1 both stimulate the production of IL-6 by monocytes, lymphocytes, mesothelial cells, fibroblasts, and adipocytes. IL-6, IL-1, and TNF-α in turn each activate the acute phase protein response in the liver, which induces hepatic production of C-reactive protein (CRP) and downregulates albumin production. Enhanced inflammation may contribute to depression via neuroinflammation, alterations in various neurotransmitter pathways, and activation of the hypothalamus-pituitary-adrenal axis. Inflammation-mediated cardiovascular disease may also explain associations between depression and cardiovascular events and death. Elevated high-sensitivity CRP, which is used for cardiovascular risk stratification, may be associated with these outcomes due to confounding factors such as smoking and diabetes mellitus in patients with CKD and ESKD, but some studies suggest that CRP and other inflammatory cytokines may have a pathophysiological role in vascular damage via the activation of inflammatory endothelial pathways, increased sympathetic activity, increased cell adhesion molecules, and decreased insulin sensitivity. Inflammatory cytokine networks are complex and interrelated, so consideration of these elevated biomarkers without the context of their soluble receptors or other cytokines in the inflammatory pathways likely oversimplifies these relationships. Nonetheless, studies have consistently shown relationships between elevated IL-6, CRP by the traditional or high-sensitivity assay, and albumin with depression, cardiovascular outcomes, and death in patients with CKD and ESKD, suggesting that these cytokines may be promising therapeutic targets to improve outcomes in these populations.

depression measurement scales for individual studies may influence the results. It is also unclear whether some of the symptoms measured by the BDI and other depression scales such as insomnia, fatigue, and changes in appetite may be a result of kidney disease itself, which is known to be associated with inflammation, rather than similar symptoms caused by depression. The included studies used variable scales and cutoffs to define depression, which may have diminished the differences in inflammatory biomarkers seen between depressed and nondepressed individuals. Despite this, we identified associations between the presence of depression and lower albumin and higher CRP and IL-6 levels, suggesting that these findings are likely robust. Most of the included studies lacked adjustment for covariates, so it is unclear whether the associations that were seen could be accounted for by age, dialysis vintage, body mass index, comorbid medical conditions, protein–energy wasting, or other possible confounding factors. Larger studies controlling for these variables will be important to further detail the relationships between these factors and determine whether confounding variables might account for the variability in the results seen in prior studies.

CONCLUSION

These data strongly support that there may be a relationship between protein–energy wasting, particularly pathways mediated by IL-6 and CRP, and depressive symptoms in patients with kidney disease. Future studies investigating the relationships between depression and protein–energy wasting in patients with CKD and ESKD should be adequately powered, include measurements of multiple biomarkers at baseline and after any intervention, and use criterion standard definitions of depression as well as continuous measures of depressive symptoms. Ideally any clinical trials would include clinically appropriate doses and

treatment durations of any therapy for depression, as well as a control group to determine whether antidepressant therapy affects biomarkers or whether any changes could be accounted for by the natural course of the disease. A proposed conceptual model describing the relationship between inflammation, protein–energy wasting, and depression in patients with CKD and ESKD is shown in Figure 4.[19,74–76]

Many important knowledge gaps remain regarding the association of depression with protein–energy wasting and inflammation in CKD and ESKD, their relationship to outcomes, and the impact of various treatment regimens on depressive symptoms, inflammatory biomarkers, and long-term morbidity and mortality. As more research is done, it will be important to gather the molecular data to better identify patients who may benefit from traditional antidepressant therapy or anti-inflammatory–based treatment regimens. Understanding the relationship between depression and inflammation may be a key next step to identify patients with CKD and ESKD who are at risk of depression or who may variably respond to existing therapies.

DISCLOSURE

MT has served as an advisor or consultant to the following organizations: Allergan Sales LLC, Alkermes, Arcadia Pharmaceuticals Inc., AstraZeneca, Axon Advisors, Bristol-Myers Squibb Company, Eli Lilly and Company, Evotec, Johnson & Johnson, Lundbeck, MedAvante, Merck, MSI Methylation Sciences Inc., Nestle Health Science-Pamlab Inc., Naurex, Neuronetics, One Carbon Therapeutics Ltd., Otsuka Pharmaceutical Co., Ltd., Roche Products Ltd., SHIRE Development LLC, Takeda Pharmaceutical Co., Ltd., and Tal Medical/PureTech Ventures. All the other authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Figure S1. Funnel plots for underlying data used for comparisons of inflammatory biomarkers in CKD or ESKD samples with vs. without depression.

Figure S2. Funnel plots for underlying data used for correlations of the severity of depression with inflammatory biomarkers in CKD and ESKD patients.

Figure S3. Correlations of depressive symptoms, taken continuously, with (A) albumin, (B) CRP, (C) hsCRP, (D) IL-6, and (E) TNF-α.

Table S1. Underlying data used for comparisons of inflammatory biomarkers in CKD or ESKD samples with vs. without depression, presented as mean (SD).

Table S2. Underlying data used for correlations of the severity of depression with inflammatory biomarkers in CKD and ESKD patients, presented as Spearman or Pearson rho.

Supplementary File (Word)

PRISMA Checklist.

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