

A Systematic Review and meta-analysis of the Evidence on Inflammation in Depressive Illness and Symptoms in Chronic and End Stage Kidney Disease

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Abstract

Background

Depression affects approximately 27% of adults with Chronic Kidney Disease (CKD) and End Stage Kidney Failure (ESKF). Depression in this population is associated with impaired quality of life and increased mortality. The extent of inflammation and the impact on depression in CKD/ESKF is yet to be established. Through a systematic literature review and meta-analysis, we aim to understand the relationship between depression and inflammation in CKD/ESKF patients.

Methods

We searched nine electronic databases for published studies up to January 2022. Titles and abstracts were screened against an inclusion and exclusion criteria. Data extraction and study

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quality assessment was carried out independently by two reviewers. A meta-analysis was carried out where appropriate, otherwise a narrative review of studies was completed.

Results

Sixty studies met our inclusion criteria and entered the review (9481 patients included in meta-analysis). Meta-analysis of cross-sectional associations revealed significantly higher levels of pro-inflammatory biomarkers; C-reactive protein (CRP); Interleukin 6 (IL-6) and Tumor necrosis factor alpha (TNF- α) in patients with depressive symptoms (DS) compared to patients without DS. Significantly lower levels of anti-inflammatory cytokine Interleukin 10 (IL-10) were found in patients with DS compared to patients without DS. Considerable heterogeneity was detected in the analysis for most inflammatory markers.

Conclusion

We found evidence for an association of higher levels of pro-inflammatory and lower anti-inflammatory cytokines and DS in patients with CKD/KF. Clinical trials are needed to investigate whether anti-inflammatory therapies will be effective in the prevention and treatment of DS in these patients with multiple comorbidities.

Introduction

Chronic Kidney Disease (CKD) is a persistent decline of the kidney function and or urinary abnormalities such as haematuria and proteinuria for over three months and affects 10% to 15% of the world population¹. The most severe stage is called End Stage Kidney Failure (ESKF), when patients will require haemodialysis, peritoneal dialysis or kidney transplant^{2, 3}. The prevalence of CKD and ESKF has been rising over the last 18 years and is anticipated to double by 2030-2040^{4 5}. The aetiology of CKD and ESKF most commonly involves diabetes (type 1 and 2) and hypertension³ and, to a lesser extent auto-immune and infectious diseases, environmental pollution^{6 7} and genetic conditions. .

Around 27% of CKD/ESKF patients have depression⁸. Depression among CKD/ESKF patients seems to be associated with early initiation of dialysis and an increased mortality compared to those without depression^{9 10}. Preventing, diagnosing, and treating depression in this population is challenging. Research guidance is inconclusive due to small sample sizes, the inclusion of individuals with different aetiologies of disease or types of dialysis, and a lack of appropriate control groups. Evidence for the efficacy of antidepressant medication in patients with CKD/ESKF and depression is poor as these patients are generally excluded from trials due to concerns about safety and adverse events. There are also reports that Selective Serotonin Reuptake Inhibitors (SSRIs) may not be effective in this population¹¹ and there is sub-optimal management of antidepressant medication in the dialysis population in the UK¹².

It has been reported that CKD patients suffer from chronic inflammation and impaired oxidative systems which worsens progressively with the stages of renal failure¹³. There is growing evidence that inflammation may lead to depressive symptoms and depressive disorders. While comorbidity of CKD and ESKF with depression is evident, it is unclear whether inflammation is more prevalent in individuals with depression and CKD/ESKF

individuals compared to individuals with CKD/ESKF, who do not have depression. If proven, such findings would highlight potential benefit of prevention and treatment strategies for depression that targets inflammation. Clinicians need better guidance on treating depression in ESKF patients, taking account of comorbidities and associated inflammation as a contributing factor.

We conducted a systematic review and meta-analysis on inflammation and depression in patients with CKD/ESKF to clarify the evidence base on the relationship between depression and CKD/ESKF and to identify inflammatory biomarkers associated with depression in CKD/ESKF patients.

Methods

The review was conducted in accord with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines¹⁴, and registered on PROSPERO on 28th August 2019 (CRD42019141305)¹⁵.

Search strategy

A sample search is shown in supplement document. The search was initially run in May 2019 and re-run in September 2020 and January 2022, where 2 eligible studies were identified for inclusion. We searched electronic databases (PubMed, Embase, MEDLINE, PsychINFO/PsychArticles, Scopus, Web of Science, CINAHL and Cochrane CENTRAL) for published studies from inception of database up to 19 January 2022, using a search strategy developed with an information scientist. To optimise the capture of relevant research, the first 200 relevant publications from Google Scholar were also considered¹⁶. Controlled (MESH terms) and text entries were used across all electronic databases (see supplement document for

MESH terms used). Databases such as DARE, ETHOS, OATD, NICE and PROSPERO were checked for existing or ongoing reviews prior to database searches. Forward and backward citation tracking was undertaken for studies that entered the review and progressed to data extraction.

Inclusion and exclusion criteria

Inclusion and exclusion criteria were set out using the Population, Exposure, Comparison, Outcome (PECO) framework ¹⁷. The criteria were developed with clinical and research experts and Patient and Public Involvement (PPI) representatives. The review includes studies of (a) adult patients (≥ 18 years) with ESKF or CKD, (b) data on pro and anti-inflammatory biomarkers (c) depression measured by standardised clinical interviews, or by administered or self-report validated psychometric instruments. We included case-control, cohort (prospective and retrospective), and cross-sectional studies; and non-randomised intervention studies and randomised controlled trials (RCTs). Exclusion criteria included preclinical studies, non-English language studies and studies published in non-peer reviewed journals. Studies investigating the effects of antidepressants or supplements on inflammation, which did not provide baseline data on inflammation in depressed and non-depressed patients were excluded. Given the sparsity of evidence, we excluded studies of kidney transplant or acute kidney injury patients.

Study selection

References, titles and abstracts from electronic database searches were exported into Rayyan QCRI ¹⁸. Titles and abstracts were screened independently by two reviewers (SJa and SJe). Screening of titles and abstracts against the inclusion and exclusion criteria was piloted

on the first 100 abstracts and revealed that in 50% of publications, information on inflammatory biomarkers was not mentioned in the abstract. Therefore, abstracts meeting all other inclusion criteria underwent full text screening. Full text articles were checked independently by SJa and SJe against the inclusion and exclusion criteria. Authors of studies and potentially relevant conference abstracts were contacted to secure full text articles. After one month to respond, one re-contact was attempted. Inter-rater reliability for the full-text screening indicated good agreement between reviewers (κ 0.89). Uncertainties were resolved by consensus and unresolved discrepancies were referred to a third reviewer (KB).

Data extraction

A data extraction table was piloted on 10 studies and refined (see supplement document for data extraction fields). Study data were extracted independently by two reviewers (SJa and SJe) and charted in an Excel spreadsheet. Study characteristics extracted included study authors, year published, sample description, methodological characteristics, demographics (age, gender, ethnicity), depression definition and cut-off scores, type and levels of inflammatory biomarkers and main results. Statistical information extracted included means/medians, standard deviations/range/interquartile range for outcome and exposure of interest, N for depressed and non-depressed groups, test-statistic and p-values. Discrepancies were discussed and resolved between the two reviewers (95.2% agreement). If data was not available on the outcome/exposure of interest, then corresponding authors were contacted and those that responded within a month were included in the meta-analysis.

Methodological quality and risk of bias

The risk of bias was assessed independently by two reviewers (SJe and SJa). Study quality and risk of bias are presented in supplementary material. RCT's were assessed using the 'Risk of Bias 2' (RoB 2) ¹⁹, Non-randomised interventional studies (NRIS) were assessed using the 'Risk Of Bias In Non-randomized Studies - of Interventions' (ROBINS-I) ²⁰.

The Newcastle-Ottawa Scale (NOS) was used to assess the quality of cohort studies (CS) ²¹. Study quality is rated as good, fair, or poor across selection, comparability and exposure categories. Studies were awarded one point for ascertainment of exposure if information was provided on how inflammatory biomarkers were measured. For assessment of outcome, studies were awarded one point if depression was diagnosed through a structured clinical interview or if data was obtained from medical records; no points were allocated for self-report measures or no description.

Cross-sectional studies (CSSs) were assessed using the AXIS tool designed specifically for CSSs ²². The tool does not provide a numerical score but allows the reviewer to assess each individual aspect of study design based on to give an overall judgment of study quality. Cohort studies from which cross-sectional data from one time-point were used, were assessed on the AXIS tool.

Data analysis

Where number of studies permitted a meta-analysis was conducted, otherwise, a narrative synthesis of the studies was undertaken (overview of narrative synthesis is presented in supplementary materials).

Meta-analysis

Studies providing baseline or longitudinal data on cytokine levels in patients with or without depression were included in the meta-analysis and in bivariate subgroup analysis. A minimum of three studies per inflammatory marker were considered sufficient for meta-analysis²³. For continuous data outcomes a weighted mean difference and 95% confidence intervals (CIs) were calculated using a random effects model which also allows suspected heterogeneity between studies²⁴. Forest plots were generated, and pooled effect sizes were calculated using Comprehensive Meta-Analysis (CMA, version 3)²⁵. The standardised mean-difference (SMD) was computed from studies providing means and standard deviations (SD) for cytokine levels in patients with or without depression. Where required SD were calculated from CIs or standard errors (SE) using a verified formula²⁶. If a study provided a median, interquartile range (including the first and third quartile) and sample size, this was converted into an estimated sample mean and SD using a formula²⁶. Where studies provided a correlation coefficient and a sample size instead of a means and SD, this was entered into CMA to compute the effect size. Where studies did not provide means and SD or correlation coefficient a standardised or unstandardised regression coefficient with SD and sample sizes for patients with or without depression with 95% CIs, were entered into CMA to compute the effect size²⁷. All effect sizes were calculated such that positive values demonstrate higher levels of inflammatory markers in depressed patients, and negative values indicated the opposite. Where adequate data was not provided, study authors were contacted for additional data and were given 3 weeks to respond. Ten percent (5/50) of authors contacted provided the additional data required for the study to be included in the meta-analysis.

Quality check

To investigate heterogeneity, subgroup and sensitivity analysis were carried out for all inflammatory markers. Within group heterogeneity was assessed using Higgin's I^2 with a $\geq 50\%$

cut-off for ‘substantial heterogeneity’²⁶. Cochrane’s Q with p values <0.05 was also reported to indicate significant within and between group heterogeneity. Likely sources of heterogeneity investigated included the way in which depression was defined (structured clinical interview or validated self-report depression tool) and the type of data provided by studies which was used to calculate the effect size. Sensitivity analyses was carried out on study design for each inflammatory marker (cross-sectional; longitudinal; RCT) and study quality (poor; fair; good).

Meta-regression investigating age, gender and ethnicity was considered for inflammatory markers with more than 10 studies, however, this data was reported for the total sample rather than for patients with or without depression rendering it inappropriate²⁶. Publication bias using Egger’s test for funnel plot symmetry was assessed for inflammatory makers containing more than 10 studies (CRP; IL-6; TNF-a). In all analyses, statistical significance was set at $p \leq 0.05$.

Results

A meta-analysis was conducted in a search which yielded 9001 citations (see PRISMA, Figure 1). Fifty-three studies met our inclusion criteria, and seven additional studies were identified by citation tracking: 60 entered the review.

Study characteristics

Studies which are included in the review are outlined in supplementary Table 1. One study used an RCT design and reported depression severity in comparison with controls²⁸. Three were cohort (CS), and 56 were cross-sectional (CSS). Most studies included haemodialysis (HD) patients (32/60), followed by mixed sample of HD and Peritoneal dialysis (PD) patients (11/60), PD patients (12/60), CKD patients (3/60) and mixed sample of CKD and HD or PD patients (2/60).

Majority of studies used a self-report depression scale to measure the presence of depressive symptoms or severity (52/60). CRP was measured most often (53/60), followed by IL-6 (25/60), TNF-a (12/60), IL-10 (7/60) and a range of other biomarkers (IL-1 β , fibrinogen, IL-17, IL-18 and IL-12p70; (note hs-CRP and CRP are referred to as CRP). Thirty (30/60) specifically aimed at investigating the association between inflammatory markers and depression in CKD/ESKF patients or an intervention and are referred to as 'fit for purpose' (supplementary table 1). Forty-eight percent of studies (29/60) reported that patients with active infections and/or inflammatory illnesses were excluded. Seventeen percent of studies (10/60) excluded patients on anti-inflammatory medication, majority of studies did not report this information. Study quality is presented in supplementary table 2.

Cross-sectional meta-analyses

Meta-analysis of cross-sectional associations between CRP and depression

Fifty-one studies analysed cross-sectional data on major depression (MD) or depressive symptoms DS and CRP levels (8370 patients). Overall, there was significantly elevated level of CRP in those with depression compared to those without depression (SMD = 0.50 [95% CI 0.28-0.72]; $p < 0.0001$) (figure 2). There was significant heterogeneity ($I^2 = 95\%$; $\text{Chi}^2 = 1046.47$, $\text{df} = 50$; $p < 0.0001$; $\text{Tau}^2 = 0.76$). Seven (7/51) used a structured clinical interview to diagnose MD, while most studies (44/51) used a self-report screening tool to measure DS. Amongst these seven studies (613 patients) which used structured clinical interview to diagnose depression, overall CRP levels had only a trend significance between MD and non-MD groups (SMD = 0.56 [95% CI -0.043 – 1.16]; $p = 0.08$), with moderate significant heterogeneity ($I^2 = 55\%$; $\text{Chi}^2 = 13.44$, $\text{df} = 6$; $p = 0.037$; $\text{Tau}^2 = 0.07$) (supplementary table 3) ²⁹⁻³⁵. Four (4/7) were fit for purpose. Numbers of MD patients included from all studies were small and ranged from 10-47 individuals.

Amongst studies which used self-report tools as diagnostic for depressive symptoms, 44 analyses of (from 40 studies; 7757 patients) found significantly higher levels of CRP in the group with DS compared to no DS group (SMD= 0.49 [95% CI 0.25-0.73]; $p<0.001$)²⁹⁻⁷³. Significant heterogeneity was detected ($I^2=96\%$; $\text{Chi}^2=1032.71$, $\text{df}=43$; $p<0.0001$; $\text{Tau}^2=0.79$). There were no between-group differences when comparison only retained studies using structured clinical interviews for MD or a validated self-report measure of depressive symptoms ($Q\text{-value}=0.47$, $\text{df}=1$; $p=0.83$). There was no difference for total between-group heterogeneity when comparing effect size calculation formats (supplementary table 5) or study quality (supplementary table 6).

Meta-analysis of cross-sectional associations between IL-6 and depression

Twenty-nine analyses from 27 studies (5140 patients) were appropriate for inclusion in the meta-analyses investigating cross-sectional associations between IL-6 and depression^{28 32 33 35 37 38 40 44-48 54 55 57 59 60 67 69 74-80}. Overall, there was significantly higher levels of IL-6 in patients with depression compared to patients without depression (SMD = 0.67 [95% CI 0.35-0.99]; $p<0.001$). There was significant heterogeneity ($I^2=96\%$; $\text{Chi}^2=696.72$, $\text{df}=28$; $p<0.001$; $\text{Tau}^2=0.71$) (figure 3). Four studies (317 patients) used a structured clinical interview to diagnose MD. Amongst these, no significant differences in IL-6 levels were found between MD and non-MD groups (SMD= 0.23 [95% CI -0.66 – 1.12]; $p=0.62$)^{32 33 35 74}; and no significant heterogeneity ($I^2=0\%$; $\text{Chi}^2=1.10$, $\text{df}=3$; $p=0.78$; $\text{Tau}^2=0.00$). Sample sizes of patients with depression were very small in all (9 to 11 people with MD)^{32 33 74}. Among studies which used self-report depressive symptoms, twenty-five analyses (from 22 studies; 4823 patients) found significant differences in IL-6 levels in individuals with increased depressive symptoms compared to no depressive symptoms (SMD = 0.74, $\text{CI}^{95}=-0.39 – 1.08$, $p<0.001$)^{28 37 38 40 44-48 54 55 57 60 67 69 75 76 78-82}. All 25 analyses showed significant considerable heterogeneity ($I^2=97\%$;

$\text{Chi}^2=692.92$, $\text{df}=24$; $p<0.001$; $\text{Tau}^2=0.75$) (supplementary table 3). Comparison of total between group heterogeneity comparing structured clinical interviews with depression defined using a validated self-report measure reported no significant heterogeneity ($\text{Chi}^2=1.08$, $\text{df}=1$; $p=0.30$).

Significantly higher IL-6 levels in depressed were found irrespective of how effect sizes were calculated and there was significant heterogeneity (supplementary table 5). Regardless of study design, both cross-sectional and RCT data reported significantly higher IL-6 levels in MD/DS compared to non- MD/DS groups (supplementary table 4). Significant considerable heterogeneity was reported for cross-sectional studies but not RCT's, furthermore total between group heterogeneity was found to be significant when comparing cross-sectional to RCT's. Only good quality cross-sectional studies (21 analyses) reported significantly higher levels of IL-6 in depressed compared to non-depressed groups (supplementary table 4)^{32 35 37 38 44-48 54 59 60 67 69 74-77 79 80}. These results were not replicated in fair quality studies^{33 55 57 78}; both fair and good quality studies reported considerable heterogeneity.

Meta-analysis of cross-sectional associations between TNF-a and MD/DS

Eleven analyses from 11 studies (1838 patients) were included in the meta-analyses^{32 33 35 44-46 48 50 59 74 80}. Overall, these found a trend for higher TNF-a levels in the MD/DS group compared to non-MD/DS group ($\text{SMD}= 0.38$, [95% CI -0.02-0.78]; $p=0.07$). All 11 analyses showed significant heterogeneity ($I^2=93\%$; $\text{Chi}^2=139.03$, $\text{df}=10$; $p<0.001$; $\text{Tau}^2=0.4$) (figure 4).

Four studies (317 patients) used a structured clinical interview to diagnose MD. These found no significant differences in TNF-a levels between MD and non-MD group ($\text{SMD}= 0.01$ [95% CI -0.72–0.73]; $p=0.99$)^{32 33 35 74}. The 4 analyses showed no significant differences in heterogeneity ($I^2=0\%$; $\text{Chi}^2=2.22$, $\text{df}=3$; $p=0.53$; $\text{Tau}^2=0.00$) (supplementary table 3). The

sample sizes of depressed patients were very small in all (9-11 MD individuals)^{32 33 74} but in one study⁸³.

Among studies which used self-report depressive symptoms (1521 patients), there was significantly higher levels of TNF in the high depressive symptoms group compared to the no depressive symptoms (SMD= 0.59 [95% CI 0.07 – 1.12]; p=0.03)^{44-46 48 50 59 80}. All 7 analyses showed significant heterogeneity ($I^2=96\%$; $\text{Chi}^2=136.58$, $\text{df}=6$; $p<0.0001$; $\text{Tau}^2=0.51$) (supplementary table 3).

Comparison of studies defining depression using structured clinical interviews with those using a validated self-report measure reported no significant heterogeneity ($\text{Chi}^2=1.65$, $\text{df}=1$; $p=0.20$). The type of effect size did not account for the findings (supplementary table 5). Both fair and good quality studies reported non-significant findings in TNF- α levels between MD/DS and non- MD/DS groups with significant heterogeneity reported for good quality studies (supplementary table 4).

Meta-analysis of cross-sectional associations between IL-10 and depression

Six analyses from 6 studies (1427 patients) were appropriate for inclusion in the meta-analyses investigating cross-sectional associations between IL-10 and depression^{44-46 50 55 59}(figure 5). All used a validated self-report measure to define the high depressive symptoms group. IL-10 levels were significantly lower in the DS compared to the non-DS group (SMD= -0.57 [95% CI -1.09-0.06]; $p<0.0001$). All 6 analyses showed significant heterogeneity ($I^2=95\%$; $\text{Chi}^2=95.02$, $\text{df}=5$; $p<0.0001$; $\text{Tau}^2=0.38$). Effect size calculation format showed no effect on the findings, however significant heterogeneity was reported only for effect size calculations using means and SD (supplementary table 5). Only good quality studies (5

analyses) reported significantly lower levels of IL-10 in depressed compared to non-depressed groups (supplementary table 4) ^{44-46 50 59}.

Meta-analysis of cross-sectional associations between IL-1B and depression

Three analyses from three studies (1086 patients) were appropriate for inclusion in the meta-analysis ^{45 46 59}(supplementary figure 1). All used a validated self-report tool to define depressive symptom group. There were no significant differences in IL-1B levels in high compared to the no-depressive symptoms group (SMD= -0.01 [95% CI -0.13-0.11] p=0.093). All 3 analyses showed no significant heterogeneity ($I^2=0\%$; $\text{Chi}^2=0.98$, $\text{df}=2$; $p=0.61$; $\text{Tau}^2=0.00$) and were of good quality. Effect size calculation format reported no significant influence on reported IL-1B levels in depressive symptoms compared to no-depressive symptoms groups (supplementary table 5).

Meta-analysis of cross-sectional associations between fibrinogen and depression

Three analyses from 4 studies (297 patients) were appropriate for inclusion ^{38 50 84}(supplementary figure 2). All used a validated self-report measure to define the depressive symptoms group. Significantly higher levels of fibrinogen were reported in high depressive symptoms compared to no-depressive symptoms group (SMD= 0.64, [95% CI 0.33-0.95]; $p<0.0001$). There was no significant heterogeneity ($I^2=35\%$; $\text{Chi}^2=4.67$, $\text{df}=3$; $p=0.19$; $\text{Tau}^2=0.036$). Effect size calculation format showed no effect (supplementary table 5).

Longitudinal associations between depressive symptoms and inflammatory cytokines

Narrative Synthesis

There were three longitudinal studies which investigated inflammatory markers and future depressive symptoms^{36 46 84}. There weren't sufficient studies for each inflammatory marker for meta-analysis, thus a narrative review was executed.

All studies were similar in terms of dialysis modality (HD patients), depression definition (Becks Depression Inventory; BDI) and percentage of females (ranging from 39.4% - 41%). There was one fit for purpose study (Haverkamp et al., 2019) that investigated whether higher levels of inflammation were associated with the development of future depressive symptoms in CKD/ESKF patients⁴⁶. They found that CRP was an independent predictor for an increase in DS. Patients with higher baseline serum CRP levels, compared to patients with lower serum CRP levels, had increased depressive symptoms at 12-months, but not at 6-months follow up⁴⁶. Haverkamp et al. 2019⁴⁶ found no significant longitudinal associations between DS, as measured by BDI, and IL-6, TNF- α , IL-10 and IL-1 β ⁴⁶. Barros, Costa, Mottin and D'Avila (2016)³⁶ did not report a change of inflammatory levels and association with worsening depression in HD patients. Bossola et al. (2012)⁸⁴ reported that fibrinogen levels are not associated with increased depressive symptoms at follow-up in HD patients. In cross-sectional analysis, both Barros et al. (2016)³⁶ and Haverkamp et al. (2019)⁴⁶ reported significantly higher CRP levels in DS patients at the 12-month follow up compared to the no DS group.

Discussion

Depression is the most prevalent psychosocial factor in patients with CKD/ESKF and is associated with increased morbidity and mortality⁸⁵. Accumulating evidence suggests that inflammation may be causal to the development of depressive symptoms in people without chronic physical illnesses⁸⁶. Whether inflammation has a role in depressed CKD/ESKF patient

is not yet clear. Higher levels of inflammation may point towards those who may particularly benefit from preventive approaches and better inform treatment strategies for depression.

Previously, one systematic review and meta-analysis investigated depression and protein energy wasting in kidney disease⁸⁷. The review only included studies with the biomarker albumin (protein-energy wasting biomarker) as well as other inflammatory markers, studies not including albumin were excluded from the review. Therefore, several studies investigating inflammatory biomarkers included in the current review were not investigated previously. Furthermore, the current review has carried out subgroup and sensitivity analyses, exploring possible sources of heterogeneity, which were not investigated previously. This is the first systematic review and meta-analysis specifically investigating inflammatory biomarkers in depressed patients with CKD/ESKF. We found evidence of higher levels of pro-inflammatory cytokines and acute inflammatory markers e.g. CRP, IL-6, TNF, fibrinogen, but not for IL-1 β , and lower levels of the anti-inflammatory cytokine IL-10 in CKD patients with increased depressive symptoms in cross-sectional studies. Pooled studies were statistically significant for higher CRP and IL-6, and a trend for TNF in CKD/ESKF patients with major depression/depressive symptoms. There was only a trend significant association for higher levels of CRP and clinical depression, and not for the other inflammatory markers. Similar results were also reported in an umbrella review of depression and peripheral inflammatory biomarkers in a population without chronic illness⁸⁸. Lee et al. (2021), reported significant association between increased depressive symptoms and CRP, IL-6 and TNF, however this association was no longer significant with chronic MD patients. In the current review there was only one study which investigated whether inflammation predicted development of depressive symptoms in patients with CKD and this found a positive association between baseline CRP and depressive symptoms at 12-months.

Most studies investigated inflammatory markers using self-report tools for depressive symptoms. Fewer studies, a total of 7 for CRP, and 4 for IL-6 and TNF - investigated cross-sectional associations using structured clinical interviews to diagnose depression. Most of these studies had very few patients and did not find associations between inflammatory cytokines and major depression. Reasons for this is most likely lack of power. Inflammation is observed in ~30% of patients with major depression in the absence of chronic physical illness⁸⁹, and in ~50% of patients with ESKF⁹⁰. Among the few studies which used structured clinical interview to diagnose depression, number of depressed patients were small (range 10-47 for CRP and even fewer for other markers), which would have limited our power to detect associations. More generally, there is an absence of studies that looked at inflammatory markers and major depression in CKD. No studies investigated the effect of starting dialysis on inflammation and the association with depression. There is variation between studies on when inflammatory parameters were collected in relation to time of dialysis. It is possible that inflammatory levels vary considerably before, during and after dialysis.

Longitudinal studies are lacking in CKD/ESKF. There were three longitudinal studies of inflammatory markers and depressive symptoms, and only one particularly investigated whether inflammatory markers at baseline predict development of future depressive symptoms⁴⁶. Haverkamp et al. (2019) found a positive association for CRP, but not other inflammatory markers and future depressive symptoms⁴⁶. They also included patients with acute infection, which may have skewed the results. Barros et al. (2016)³⁶ did not report on longitudinal associations of inflammatory markers at baseline and future depressive symptoms. In individuals without chronic physical illnesses, there is evidence that chronic inflammation predicts depressive symptoms^{91 92}. More research is needed to investigate whether inflammation is a shared pathway partly explaining the high prevalence of depression in the chronic physically ill, and in CKD/ESKF specifically. Indeed, ESKF commonly arises in patients

experiencing hypertension and diabetes; and depressive illness is known to be a co-morbid complication of medical disorders. There is the need for higher quality, larger, longitudinal studies for evidence to be conclusive of the role of inflammation in CKD/ESKF patients with depression.

We identified marked heterogeneity in study designs, but overall, the type of outcome measure used (self-report vs structured instrument), duration and method of dialysis, methods to measure effect size appeared to have some influence. There were no studies that reported whether dialysis efficacy or duration was associated with higher inflammation and depression. Future studies should focus on CRP, IL6, and TNF and more explicitly investigate whether there are co-morbid medical conditions and include measures of a range of severity of depressive illness in ESKF. The timing of onset of depressive illness is also important to clarify, as a previous history of depression may predispose to later depression in the face of a medical condition or life event with little specificity for ESKF and related inflammation. Our study could not investigate cause or effect as most studies were conducted cross-sectionally. It is possible that depressive symptoms triggered increased inflammation. Both directions have been seen in the literature. Indeed, histories and contemporary experiences of adversity and trauma also make depression more likely and raise inflammatory markers. Furthermore, ESKF and dialysis are demanding and may lead to adjustment reactions, and pessimism that may not meet criteria for depression but may reflect other life stressors, such as social isolation, fear of loss and death, concerns about dependents, and uncertainty, not to mention the need for lifetime dialysis and a schedule which is dictated by health needs. This will make enjoyment of everyday life more difficult, for example, taking holidays or travel and risks of new onset conditions complicating an already challenging medical condition. Psychological flexibility and adjustment to the diagnosis and treatment are predictors of better outcomes and might be the mechanism by which therapeutic efforts might be helpful ⁹³. Indeed, acceptance and commitment therapy encourages

psychological flexibility and is being tested in many chronic conditions including cancer survivors, and may have a place in the care of dialysis patients living with uncertainty ⁹⁴.

Limitations

There is limited evidence and few studies that reported on the same inflammatory markers using similar sample sizes. Longitudinal and experimental studies are needed, testing whether inflammation is a shared factor for the development of depression and chronic physical illnesses which could be a target for prevention. Many studies reported here were not fit for purpose. Most studies were not designed to evaluate our research questions. With the primary cause of CKD/ESKF being diabetes or hypertension, it has been reported that medications taken for these conditions have anti-inflammatory properties⁹⁵⁻⁹⁷. The studies included in this review did not specify medications taken by patients, therefore the effect this could have on inflammatory markers is unknown.

It is still unknown whether inflammation is particularly associated to a particular aetiology of CKD/ESKF and depression. There is a need for psychological interventions, social support, and anti-inflammatory drugs to investigate its effects on inflammation to observe whether inflammation could be a mechanism. Larger multicentre studies are needed focusing on specific patient groups, and those with specific co-morbidities⁹⁸. Lastly, it is important to mention in this context directionality of the relationship. As most studies presented here were cross-sectional it is still unclear in the CKD/ESKF population whether inflammation is indeed causally related to development of depressive symptoms. It is equally possible that inflammation follows depressive symptoms.

In conclusion, we found evidence for a cross-sectional association of higher levels of pro-inflammatory cytokines and depressive symptoms or clinical depression in patients with

CKD/ESKF. Research is needed to investigate whether inflammation is a target for prevention and treatment of CKD/ESKF patients with depression.

Conflict of Interests: None declared

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