Depressive symptoms in an ethnically Diverse cohort of chronic dialysis patients:

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Chapter 8

Differences in the association of inflammation and tryptophan with depression between white and non-white chronic dialysis patients

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ABSTRACT

Background

Among chronic dialysis patients, racial differences have been found in the prevalence of depressive symptoms. Depressive symptoms are associated with high levels of inflammatory markers and a lower tryptophan (TRP) concentration. It seems possible that different biochemical parameters are involved in the development of depression in white and non-white patients. Therefore, we examined whether the inflammation-depression association and the tryptophan- depression association differ between white and non-white dialysis patients and whether the association between inflammation and depressive symptoms is mediated by tryptophan degradation along the kynurenine pathway in both white Methodsand non-white patients.

Methods

We analyzed data of the DIVERS study, an multiracial and multicenter observational prospective cohort study in chronic dialysis patients in the Netherlands. Depressive symptoms were measured with the Beck Depression Inventory. Simultaneously, peripheral blood was collected before dialysis to measure inflammatory markers (HsCRP, IL-1β, IL-6, IL-10, and TNFα) and TRP and its degradation products kynurenine (KYN) and 3-hydroxykynurenine (3-OH-KYN). Linear regression was used to determine the association between inflammatory markers, TRP and depressive symptoms, stratified for white and non-white patients.

Results

In total 270 white patients and 220 non-white patients were included. The presence of depressive symptoms was significantly higher in non-white patients (51%) compared to white patients (37%) (P<0.01). Among white patients, HsCRP was significantly associated with depressive symptoms (β=0.6 (95% CI: 0.1-1.2)). Among non-white patients, significant associations with depressive symptoms were found for both HsCRP (β=1.0 (95% CI: 0.1-2.0)) and IL-6 (β=2.6 (95% CI: 0.8-4.4)). TRP levels were only significantly associated with depressive symptoms in non-white patients (β=-0.3 (95% CI: -0.4- -0.1)). TRP degradation along the KYN pathway did not mediate the association between inflammatory markers and depressive symptoms in either group.

Conclusion

A significantly higher presence of depressive symptoms was found in non-white than in white chronic dialysis patients. Our results indicate that for non-white and white dialysis patients different biochemical parameters are associated with depressive symptoms.

INTRODUCTION

Depressive symptoms are highly prevalent in chronic dialysis patients[1]. Racial and ethnic differences have been found in the prevalence of depressive symptoms, with a higher prevalence in black dialysis patients than in white patients[2]. This difference could be explained by social factors[3], but it may also involve biochemical markers (e.g. inflammatory markers and tryptophan (TRP)). It is not clear whether racial differences exist among chronic dialysis patients regarding the associations between inflammatory markers and depressive symptoms, and between TRP and its degradation products (e.g. kynurenine (KYN)) and depressive symptoms.

Dialysis patients are known for a chronic inflammatory state[4;5], which has often been linked to a higher presence of depressive symptoms[6]. In general population studies, indications have been found for racial differences regarding concentrations of inflammatory markers[7;8] and for the association between inflammatory markers and depressive symptoms[9;10]. Namely, higher CRP levels were found in black subjects than in white subjects[8], and significant associations between depressive symptoms and CRP were found only in white women[10] or stronger associations in non-Hispanic whites[9]. Besides high inflammatory markers, dialysis patients also have been found to have low TRP and high TRP degradation products[11;12]. Both low TRP and degradation products of TRP have been linked to depression in the general population and other medical settings[11-13]. Examining racial differences in the association of inflammatory markers and TRP with depressive symptoms may help to clarify differences in the prevalence of depressive symptoms between ethnic groups, but may also be important in order for adapting future treatment to different ethnic groups.

Inflammatory markers are linked to TRP and its degradation products through the inducible enzyme indoleamine 2,3-dioxygenase (IDO). IDO is activated by inflammatory markers, and degrades TRP into KYN[14;15] (figure 1). As TRP is a precursor of the neurotransmitter serotonine (5-HT), degradation of TRP into KYN reduces the availability of TRP for the conversion to 5-HT[16]. A low concentration of 5-HT increases the susceptibility to develop depressive symptoms[17;18]. Degradation products of KYN, in particular quinolinic acid (QA) and 3-hydroxykynurenine (3-OH-KYN), are potentially neurotoxic and may additionally contribute to the development of depressive symptoms[19]. Therefore, TRP degradation along the kynurenine pathway is one of the presumed mechanisms linking inflammation and depression[20].

The aims of this study were to examine whether white and non-white chronic dialysis patients differ regarding, first, the association between inflammatory markers and depressive symptoms and, second, the association between TRP and TRP degradation products and depressive symp-toms, but also to examine whether there are differences in the concentrations of TRP and TRP deg-radation products between white and non-white dialysis patients. The third aim was to examine whether TRP degradation along the KYN pathway explains the association between inflammatory markers and depressive symptoms in both white and non-white patients.

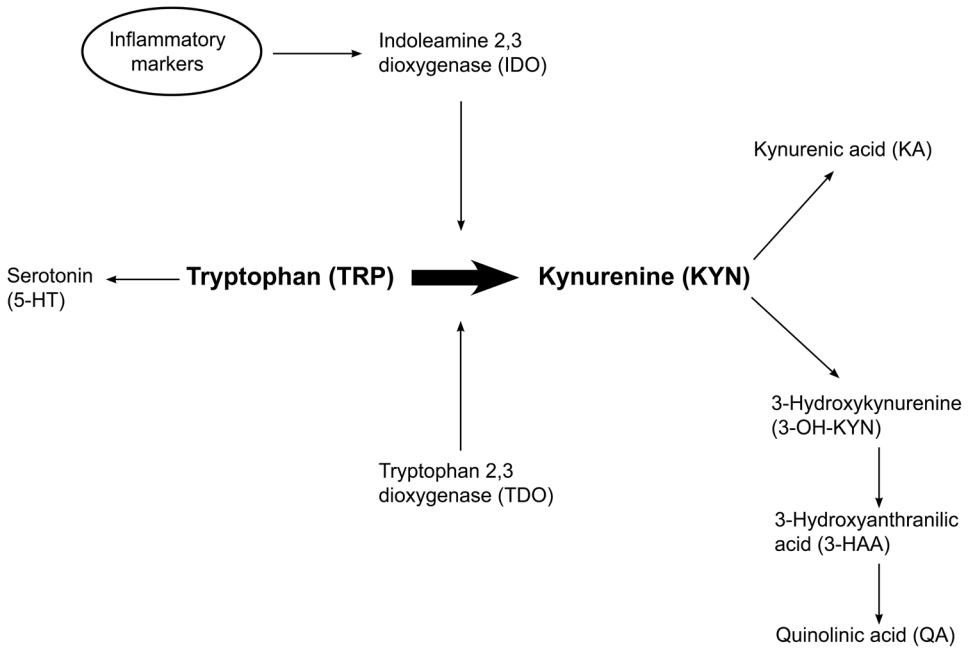

Figure 1. Tryptophan degradation along the kynurenine pathway

METHODS

Study design

We analyzed data of the DIVERS study (Depression related factors In dialysis patients with Various Ethnicities and Races Study), an observational, prospective multiracial cohort study performed in chronic dialysis patients in four urban teaching hospitals and one university hospital in The Netherlands.

Patients were eligible for the DIVERS study if they were ≥18 years of age, underwent dialysis treatment (either hemodialysis of peritoneal dialysis) for at least 90 days, were able to complete a questionnaire in either Dutch or English, and had no cognitive impairments (e.g. dementia). Hemodialysis patients were approached for study participation during dialysis treatment and peritoneal dialysis patients were approached during an outpatient appointment. Both prevalent and incident dialysis patients were included, respectively between June 2012 and December 2013 and between June 2012 and December 2014. All patients gave written informed consent before inclusion. The DIVERS study was approved by the medical ethical committees of all participating centers. The study was carried out in accordance with the Helsinki declaration of 1975, as revised in 2008.

The baseline assessment consisted of completion of a questionnaire and a blood sample, which was drawn before dialysis in hemodialysis patients and at a visit to the outpatient clinic in peritoneal dialysis patients. For the current analysis, patients were included in case of complete data on inflammatory markers (HsCRP, IL-1β, IL-6, IL-10, TNFα) and TRP degradation (TRP, KYN and 3-OH-KYN), and returned questionnaires.

Demographic and clinical characteristics

Data on socio-demographic characteristics were collected through a questionnaire: marital status, having children (yes/no), educational level, employment (yes/no), smoking (yes/no), alcohol use (yes/no), and ethnicity.

The following data were collected from electronic medical records: age, gender, dialysis modality, dialysis vintage, Body Mass Index (BMI), primary kidney disease using the European Renal Association-European Dialysis and Transplant Association (ERA-EDTA)codes[21] (Diabetes Mellitus, Glomerulonephritis, Renal vascular disease, and other), comorbidities (classified according to the Davies comorbidity index[22], indicating no, intermediate or severe comorbidity), anti-depressant use (yes/no), and residual diuresis (indicating remaining glomerular filtration rate (GFR) and defined as a urine production of >100ml per day).

Race

Race was determined based on the country of birth of the patient's parents and classified into the categories white or non-white. All patients originating from European countries were considered whites. Patients were considered non-whites if they originated from Sub-Saharan Africa, North-Africa/Western Asia (including Morocco and Turkey), South Asia/South-East Asia, and South-America/Caribbean. Surinamese patients were classified according to the country of birth of their grandparents. The use of country of birth as indicator of ethnicity is a standard approach in the Netherlands[23]. It is particularly useful in the Netherlands because most immigrants are first generation immigrants due to the short immigration history of the country (late 1970s and begin 1980s)[23].

Depressive symptoms

Depressive symptoms were measured with the Beck Depression Inventory (BDI)[24]. The BDI consists of 21-items, measuring symptoms of depression over the preceding two weeks. Items are scored on a 0-3 scale, and summed scores range from 0 to 63, with higher scores indicating more severe depressive symptoms. This questionnaire was validated in the ESRD population of one of the participating centers of this study[25]. A cut-off point of 13 was determined for the detection of depression, with a sensitivity of 0.75 and specificity of 0.90. We only used this cut-off point for descriptives (table 1), to determine the prevalence of depressive symptoms in both white and non-white patients.

Inflammatory markers

We collected peripheral blood before dialysis in anticoagulant-free EDTA tubes. All samples were immediately centrifuged at 1200 g for 10min and serum was stored in aliquots at -80 °C until analysis. The Department of Rheumatology & Clinical Immunology (University Medical Center Groningen, The Netherlands) determined pro-inflammatory cytokines (HsCRP, IL-1β, IL-6, and TNF-α) and the anti-inflammatory cytokine (IL-10) by using the Magnetic Luminex Screening or Performance assay (R&D Systems, Abingdon, UK) according to the manufacturer's instructions. Samples were measured using Luminex 100 System (Luminex, Austin, Tx, USA) and data were analyzed with StarStation software, version 2.3 (AppliedCytometry, Birmingham, UK).

Tryptophan and kynurenine

TRP, KYN and 3-OH-KYN concentrations were measured by the University Medical Center Groningen, The Netherlands (Department of Laboratory Medicine), by using an automated online solid-phase extraction-liquid chromatographic-tandem mass spectrometric (XLC-MS/MS) method with deuterated internal standards, according to described methods[26]. We determined IDO-activity (tryptophan degradation) by calculating the KYN/TRP ratio $x10^3$ (Kyn/TRP ratio).

Statistical analysis

Differences between white and non-white patients in baseline characteristics and inflammatory markers, TRP, and TRP degradation products were tested with an unpaired Student's t-test or Mann-Whitney U test for continuous data or chi-squared test for categorical data. HsCRP, IL-1β, IL-6, and IL-10 levels were log transformed because of a skewed distribution, to obtain a normal distribution.

First, the association between inflammatory markers and depressive symptoms was examined by using univariate and multivariate linear regression, stratified for white and non-white patients. We adjusted for age, gender, education, smoking, alcohol use, BMI, dialysis modality, primary cause of renal failure, comorbidities, residual diuresis, and dialysis vintage. Second, the association between TRP, KYN, 3-OH-KYN, and KYN/TRP ratio and depressive symptoms was examined, since both TRP and KYN metabolites could be involved in the development of depressive symptoms. A linear regression analysis was performed again, unadjusted and adjusted for the same potential confounders as mentioned above. Third, to examine whether tryptophan degradation along the kynurenine pathway mediated the association between inflammatory makers and depressive symptoms, this association was adjusted for the KYN/TRP ratio.

To obtain a complete dataset missing socio-demographic and clinical data and missing values on the BDI were imputed with multiple imputation techniques in SPSS (10 repetitions)[27]. Using multiple imputation missing data are imputed by a value that is

predicted using the patient's available characteristics under the assumption of missing 'at random'. Dialysis vintage in months was first square root transformed, because of a skewed distribution, to enter the multiple imputation model. All missing variables had <5% missing.

We performed a sensitivity analysis including patients who did not return their questionnaire by imputing these missing questionnaires. In a second sensitivity analysis, we subdivided the non-white patient group by region of origin (Sub-Saharan Africa, North-Africa/Western Asia, South Asia/South-East Asia, and South-America/Caribbean). Third, we performed our analysis in the hemodialysis patients only and in the prevalent patient group only.

Data analyses were performed using SPSS 21.0 (SPSS Inc., Chicago, IL, USA). P-values <0.05 were considered statistically significant.

RESULTS

Patient characteristics

A total of 548 chronic dialysis patients were included in the DIVERS study between June 2012 and December 2014. Patients without a measurement of inflammatory markers at baseline (N=41) or who did not return their questionnaire (N=17) were excluded. The study population consisted of 490 chronic dialysis patients: 270 white and 220 non-white patients. Baseline characteristics are summarized in table 1. White patients were significantly older, more often had a partner, more often used alcohol, more often had a residual renal function and had a significantly different distribution of the primary causes of renal failure than in non-white patients, especially diabetes mellitus was a less common cause in whites than in non-whites. IL-6, TRP, KYN, and the KYN/TRP ratio were significantly higher in white than in non-white patients. The presence of depression was significantly higher in non-white (51%) than in white patients (37%).

Associations between inflammatory markers and depressive symptoms

Table 2 shows the associations between inflammatory markers and depressive symptoms. In white patients univariate linear regression showed a significant association between HsCRP and depressive symptoms (β=0.6 (95% CI: 0.1-1.2)). This association remained significant after adjustment for potential confounders. None of the other inflammatory markers were significantly associated with depressive symptoms. In non-white patients significant associations were found between both HsCRP and IL-6 and depressive symptoms, respectively β=1.0 95% CI: 0.1-2.0 and β=2.6 95% CI: 0.8-4.4. After adjustment the association between HsCRP and depressive symptoms was β=1.0 (95% CI: 0.1-2.0) and between IL-6 and depressive symptoms β=2.1 (95% CI: 0.3-4.0).

Table 1. Baseline characteristics of 490 chronic dialysis patients

	Total	Whites (N=270)	Non-whites (N=220)	P-value
Socio-demographic characteristics				
Age, mean (SD)	64 (15)	69 (14)	58 (14)	≤0.01*
Gender, male %	60	61	60	0.92
Partnership, partner %	52	58	46	≤0.01*
Children, yes %	78	78	79	0.70
Education, low %	58	56	61	0.27
Employment, unemployed %	89	88	90	0.61
Smoking, yes %	19	20	17	0.45
Alcohol use, yes%	25	39	8	≤0.01*
Clinical characteristics				
Dialysis modality, hemodialysis %	89	89	90	0.80
Incident, yes %	32	33	31	0.52
Months on dialysis, median (IQ)	18 (5-49)	15 (5-43)	23 (5-62)	0.06
Body mass index kg/m2, mean (SD)	27 (6)	27 (6)	28 (6)	0.09
Residual renal function %	67	73	59	≤0.01*
Primary cause of renal failure %				≤0.01*
Diabetes Mellitus	24	13	38	
Glomerulonephritis	11	12	9	
Renal vascular disease	27	30	22	
Other	38	44	31	
Davies comorbidity score %				0.27
No	27	29	23	
Intermediate	55	54	57	
Severe	18	17	20	
Anti-depressants, yes %	10	10	11	0.86
Inflammatory markers				
HsCRP, mg/L, median (IQ)	2.4 (0.7-6.8)	2.5 (0.6-7.0)	2.3 (0.7-6.7)	0.68
IL-1β, pg/mL, median (IQ)	0.1 (0.01-0.41)	0.1 (0.01-0.41)	0.1 (0.01-0.4)	0.46
IL-6, pg/mL, median (IQ)	2.7 (1.5-4.8)	2.9 (1.7-5.4)	2.3 (1.4-4.5)	≤0.01**
IL-10, pg/mL, median (IQ)	0.3 (0.13-0.65)	0.3 (0.13-0.62)	0.3 (0.1-0.7)	0.71
TNF-α, pg/mL, mean (SD)	21.4 (12)	21.4 (13)	21.4 (10)	0.99
TRP, µmol/l (SD)	27.5 (9)	28.2 (9)	26.5 (8)	0.03*
KYN, µmol/l (SD)	4.6 (2)	4.8 (2)	4.2 (1)	≤0.01**
3-OH-KYN, nmol/l (SD)	168.7 (65)	173.6 (69)	162.8 (58)	0.06
KYN/TRP x 10^3 (SD)	172.1 (53)	177.6 (55)	165.2 (49)	≤0.01**
Depressive symptoms				
BDI>13, %	43	37	51	≤0.01**

* P ≤ 0.05, ** P ≤ 0.01

Abbreviations: SD (standard deviation), IQ (interquartile range), TRP (Tryptophan), KYN (Kynurenine), 3-OH-KYN (3-hydroxykynurenine), KYN/TRP (Kynurenine/tryptophan ratio)

Table 2. Associations between cytokines and depressive symptoms in 490 chronic dialysis patients

	Whites (N=270)		Non-whites (N=220)	
	b (95% CI) Unadjusted	b (95% CI) Adjusted for sociodemographics, lifestyle factors and medical variables	b (95% CI) Unadjusted	b (95% CI) Adjusted for sociodemographics, lifestyle factors and medical variables
HsCRP^{L}	0.6 (0.1-1.2)*	0.6 (0.1-1.2)*	1.0 (0.1-2.0)*	1.1 (0.1-2.0)*
IL-1β^{L}	-0.1 (-0.6-0.3)	-0.1 (-0.6-0.3)	0.05 (-0.7-0.8)	-0.03 (-0.7-0.7)
IL-6^{L}	0.9 (-0.1-1.9)	0.8 (-0.2-1.9)	2.6 (0.8-4.4)**	2.2 (0.3-4.1)*
IL-10^{L}	-0.5 (-1.1-0.01)	-0.5 (-1.0-0.1)	0.2 (-0.8-1.2)	0.3 (-0.8-1.3)
TNF-α	-0.03 (-0.1-0.04)	-0.03 (-0.1-0.04)	0.1 (-0.1-0.3)	0.1 (-0.1-0.3)

^{L}=Log transformed

* P ≤ 0.05, ** P ≤ 0.01

Adjusted for: age, gender, education, smoking, alcohol, BMI, dialysis modality, primary cause of renal failure, Davies comorbidity score, residual diuresis and dialysis vintage.

Abbreviations: b (Beta)

Associations between tryptophan and metabolites and depressive symptoms

Table 3 shows the associations between TRP, 3-OH-KYN, KYN, and KYN/TRP ratio and depressive symptoms. In non-white patients, TRP was significantly associated with depressive symptoms in, unadjusted β=-0.3 (95% CI: -0.4- -0.1) and after adjustment β=-0.2 (95% CI: -0.4- -0.001)). In white patients this association was not significant. KYN, 3-OH-KYN, and KYN/TRP ratio were not significantly associated with depressive symptoms in either patient group.

Table 3. Associations between tryptophan and metabolites and depressive symptoms in 490 chronic dialysis patients

	Whites (N=270)		Non-whites (N=220)	
	b (95% CI) Unadjusted	b (95% CI) Adjusted for sociodemographics, lifestyle factors and medical variables	b (95% CI) Unadjusted	b (95% CI) Adjusted for sociodemographics, lifestyle factors and medical variables
TRP	0.004 (-0.1-0.1)	-0.01 (-0.1-0.1)	-0.3 (-0.4- -0.1)**	-0.2 (-0.4- -0.001)*
KYN	0.2 (-0.4-0.8)	0.1 (-0.4-0.7)	-0.3 (-1.4-0.8)	-0.1 (-1.2-1.0)
3-OH-KYN	0.01 (-0.01-0.02)	0.01 (-0.01-0.02)	-0.01 (-0.04-0.02)	-0.01 (-0.04-0.02)
KYN/TRP	0.01 (-0.01-0.03)	0.01 (-0.01-0.03)	0.03 (-0.004-0.1)	0.02 (-0.01-0.1)

* P ≤ 0.05, ** P ≤ 0.01

Adjusted for: age, gender, education, smoking, alcohol, BMI, dialysis modality, primary cause of renal failure, Davies comorbidity score, residual diuresis and dialysis vintage.

Abbreviations: b (Beta), TRP (Tryptophan), KYN (Kynurenine), 3-OH-KYN (3-hydroxykynurenine), KYN/TRP (Kynurenine/tryptophan ratio)

Tryptophan degradation and the association between inflammatory markers and depressive symptoms

Table 4 shows the association between inflammatory markers and depressive symptoms adjusted for tryptophan degradation (KYN/TRP ratio), to examine whether tryptophan degradation explained part of this association. Adjustment for KYN/TRP ratio did not attenuate the association between HsCRP and depressive symptoms in white patients nor the association of HsCRP and IL-6 with depressive symptoms in non-white patients.

Table 4. Adjustment of the association between inflammatory markers and depressive symptoms for tryptophan degradation in 490 chronic dialysis patients

		b (95% CI) Unadjusted	b (95% CI) Adjusted for KYN/TRP
Whites	HsCRP^{L}	0.6 (0.1-1.2)*	0.6 (0.1-1.1)*
Non whites	HsCRP^{L}	1.0 (0.1-2.0)*	1.0 (0.1-2.0)*
	IL-6^{L}	2.6 (0.8-4.4)**	2.5 (0.7-4.3)**

^{L}=Log transformed

* P ≤ 0.05, ** P ≤ 0.01

Abbreviations: b (Beta), KYN/TRP (Kynurenine/tryptophan ratio)

Sensitivity analysis

Inclusion of the 17 patients that did not return their questionnaire yielded identical results, except for IL-10. Namely, we found a significant association between IL-10 and depressive symptoms in white patients (β 0.5 (95% CI: -1.0-0.0)). However, after adjustment this association lost significance.

The subdivision of the non-white patient group per region of origin resulted in 22 Sub-Saharan pa-tients, 39 North-African/Western Asian patients, 96 Southern Asia/Eastern Asian patients, and 64 South-American/Caribbean patients. Only among the South-American/Caribbean patients significant associations were found between inflammatory markers and depressive symptoms (HsCRP β=2.1 (95% CI: 0.3-4.0) and IL-6 β=4.5 (95% CI: 0.5-8.5). We found a significant association between TRP and depressive symptoms among North-African/Western Asian patients (β=-0.6 (95% CI: -1.1- -0.1), but not in the other patient groups. Compared to the total patient group, the analysis in hemodialysis patients (N=436) showed stronger associations between HsCRP β=1.4 (95% CI: 0.4-2.5)) and IL-6 β=3.3 (95% CI: 1.5-5.2)) and depressive symptoms in non-white patients, while no significant associations were found in white patients. Associations between TRP and depressive symptoms were comparable in the hemodialysis group compared to the total group. The analysis in prevalent patients (N=333) showed results that were comparable to the results for the total group, except that after adjustment the association between IL-6 and depressive symptoms was no longer significant in the non-white patients.

DISCUSSION

This observational study examined whether white and non-white chronic dialysis patients differ in respect to the associations between inflammation and depression and between TRP and depression association between white and non-white chronic dialysis patients. We found stronger associations between inflammatory markers and depressive symptoms in non-white patients compared to white patients. TRP was associated with depressive symptoms only in non-white patients.

The association between inflammatory markers and depressive symptoms has been studied frequently in dialysis patients[6], but mixed results have been found. In a review including 23 studies[6], only 11 studies found significant associations between inflammatory markers and depressive symptoms. These studies were mostly conducted in racially homogenous cohorts[28], or in cohorts consisting of mostly white patients[2;29]. However, general population studies found racial differences in concentrations of inflammatory markers[7;8] and associations with depression[10;30]. Namely, higher median CRP levels were found in black subjects compared to white subjects[8] and a cross-sectional study only found significant associations between CRP and depressive symptoms in white women[10]. These associations were stronger in non-Hispanic whites[9], while a longitudinal study found that only black patients showed a significant association between depressive symptoms and CRP 5 years later[30]. We found stronger associations between HsCRP and IL-6 and depressive symptoms in non-white dialysis patients compared to white dialysis patients. These results underline the importance of examining racially diverse cohorts and may help explain the inconsistence found in previous studies, as these studies were performed in racially differing populations.

Dialysis patients are known to have lower TRP and higher KYN concentrations than healthy subjects[11;12], probably because of increased tryptophan degradation[11]. We found slightly, but significantly lower TRP concentrations in non-white dialysis patients than in white patients, but non-white dialysis patients also had significantly lower KYN concentrations than white dialysis patients. Our reported KYN concentrations are still higher than in healthy subjects[11] and since it is known that KYN concentrations are related to TRP levels[19], the lower KYN levels in non-white patients may merely be secondary to the lower TRP levels in this group. The lower TRP concentration we found in non-white dialysis patients is not a result of increased tryptophan degradation, because tryptophan degradation was lower in non-white patients (165.2 ±49) than in white patients (177.6 ±55). As TRP is an essential amino-acid[31], it must be obtained through diet. Therefore, it is conceivable that TRP concentrations may vary between white and non-white dialysis patients because of different dietary habits.

We only found a significant association between lower TRP and more depressive symptoms in non-white dialysis patients. The stronger inflammation-depression and tryptophan-depression associations we found in non-white dialysis patients may imply that different biological processes are involved in depressive symptoms in white and non-white dialysis patients[32]. Possibly, white and non-white dialysis patients have different

etiological patterns leading to depression. These associations may also partially explain the higher presence of depressive symptoms in non-white patients (51%) than in white patients (37%). However, the pathogenesis of depressive symptoms is multifactorial, and other factors have also been proposed to explain differences between ethnic groups in the general population, for example socio-demographic factors, such as socio-economic status, educational level, and unemployment and social factors such as acculturation, discrimination, and low social support[3].

Adjustment for TRP degradation did not attenuate the association between inflammatory markers and depressive symptoms in either white or non-white dialysis patients. The same result was found in a general population study using the same methodology in patients with a current depression or lifetime risk to develop depression[20]. The authors noted that the levels of inflammation may have been too low in their general population cohort to confirm the role of tryptophan degradation, but we could also not confirm this role in a patient group known for high levels of inflammation[33]. Nevertheless, indications that tryptophan degradation plays a role in the pathophysiology of depression were found both in animal studies[34;35] and in studies among patients using interferon α therapy[36;37], which subsequently induced depression.

There are some limitations to this study. First, due to the cross-sectional design of the study we cannot determine the direction of the associations found. Second, our results may be subject to cultural bias, because the BDI questions may have been interpreted differently by patients of different ethnic groups. However, the BDI was validated in one of the participating multi-ethnic dialysis centers of the DIVERS study[25]. Third, the non-white patient group comprised a diverse population, consisting of patients from Sub-Saharan Africa, North-Africa/Western Asia, Southern Asia/Eastern Asia and South-America/Caribbean. We performed a sensitivity analysis using the subdivision of the non-white group, but these groups were too small to be examined separately. Fourth, the non-white population in European countries differs from the non-white population in the US and is therefore not directly comparable. A strength of this study is the racial/ethnic diversity of the cohort, which enabled us to report on about two almost equally large groups of white and non-white patients in an European setting. Furthermore, the availability of data on inflammatory markers, tryptophan degradation and depressive symptoms is notable.

In conclusion, the present study suggests that depressive symptoms in white and non-white chronic dialysis patients may be influenced by different biochemical parameters. These results may partially explain the higher presence of depressive symptoms in non-white patients. TRP degradation along the KYN pathway did not mediate the association between inflammatory markers and depressive symptoms in either group. Studies are needed to explore whether the difference in TRP concentration might be explained by differences in protein intake between white and non-white dialysis patients, and to identify factors that contribute to the differences in the presence of depressive symptoms between non-white and white patients.

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