Differentiating Depression from Apathy in Chronic Kidney Disease: a Prospective Study.

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Abstract

**Background.** Emotional deterioration is frequently found in patients with chronic kidney disease, but some patients are affected by depressed mood without fulfilling the criteria of a depressive disorder. Those patients might rather suffer from an apathy symptom. Apathy as a symptom of a medical disease is accompanied by loss of motivation and interest, cognitive impairments, and emotional distress. Our study tested how groups of apathetic and depressed chronic kidney disease patients responded to a single haemodialysis session on measures of mood.

**Methods.** 21 haemodialysis patients were assigned to subgroups (depressed, apathetic only, without depression and apathy) according to clinical relevant cut-offs. Sensitive questionnaires were administered to monitor mood state in general and mood changes before and after a single haemodialysis session in the chronic kidney disease patients. The results were compared to 20 age-matched healthy controls receiving no treatment.

**Results.** For the dialysis patients had either apathy or depression and seven had neither apathy nor depression. Mood state was seriously affected in all haemodialysis patients with depressed patients showing the largest effect compared to healthy controls. Patients with apathy and patients without apathy and depression were comparable in their mood state. We observed a positive mood change after the haemodialysis only in patients without apathy and depression. Their mood state improved significantly and reached nearly the level of healthy controls.

**Conclusions.** The absence of a short-term mood change in apathetic dialysis patients makes them comparable to dialysis patients with depression. We argue that apathetic patients lack the probable mood brightening effect of the haemodialysis. The lack of emotional improvement by dialysis sessions could also lead to decreased adherence of the patients. Hence, apathy seems to be a serious symptom in chronic kidney disease that is worth to be considered at least in the diagnostic process. Accompanying psychotherapeutic care for these patients would be desirable.

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**Introduction**

Depression has been identified with a prevalence of 21% and as the most common psychiatric disorder in chronic kidney disease (CKD)\[^1,2,3\]. It is an important risk factor of mortality in these patients\[^4,5\]. 10\,-\,12% of stage 5 CKD patients, i.e. patients with an end-stage renal failure requiring chronic dialysis, have an increased suicidal risk\[^6\] and an 84% higher rate of suicide than the general population\[^7\]. Furthermore symptoms of depression limit the patients’ quality of life and amplify the progression of the underlying renal disease\[^8\]. A clinical relevant depression decreases also the patients’ adherence on the requirements of the dialysis session such as restriction on fluid intake.\[^9\]

Depression is characterized by somatic, cognitive, and emotional symptoms. In CKD sleep disturbances, pain, and fatigue are common symptoms of the uraemia. The similarity to the somatic symptoms of a depression makes it difficult to determinate and contributes to false-positive diagnoses of depressions. Studies observing depressive disorders in CKD reported biased depression scores when self-report questionnaires were administered\[^10\]. These studies turned out cognitive-emotional symptoms of the depression and suicidal thoughts as the best discriminators between CKD patients with and without depression\[^9\].

Beside depressive symptoms in CKD patients the clinical impression is often marked by loss of motivation and interest and emotional distress. A simultaneous depletion of behaviour, cognition, and emotion is observed although no pronounced depression exists in these patients. We argue that apathy can describe this state of non-depressed but affective impaired CKD patients. Apathy has received different definitions in the literature. Marin defined apathy as loss of motivation and interest and differentiated between apathy as a syndrome and apathy as symptom of diseases and disorders associated with cognitive impairment, diminished level of consciousness, or disturbance of emotion \[^22,23\]. Whereas the syndrome of apathy is not attributed to states of diminished level of intellect and emotion, apathy as a symptom is related to many psychiatric, neurological, and somatic disorders. In particular apathy is symptomatic in most patients with major depression. Their apathy scores are high although a number of these patients show no symptoms of apathy\[^24\]. Research on apathy in individuals with Alzheimer’s disease\[^25\], traumatic brain injury \[^26\], and HIV-infection\[^27-29\] revealed out the same dissociation between depression and apathy. Subgroups of patients with depression without apathy, with depression and apathy, and with apathy only coexist among these populations. Symptoms of apathy were frequently associated with the cognitive impairment inherent to the disorder and expressed as a lack of motivation and the absence of self-initiated behaviour in patients’ everyday life.

Whereas the occurrence of depression in CKD and its negative impact on cognition and quality of life has been widely studied, symptomatic apathy has never been considered so far. It remains unclear whether apathy and depression could be differentiated also in CKD patients. We assume that apathetic and depressed patients independently exist among the CKD population. Apathy and depression should have different effects on the quality of life, in particular on the long-term mood state of the patients. Furthermore, symptoms of apathy and symptoms of depression should moderate the emotional reactivity to the haemodialysis treatment to a different extent. The hypothesis was tested by means of a pre-post control group design evaluating changes of mood before and after a single dialysis session.

**Material and Methods**

**Sample**

This is a secondary analysis of a study that had been published previously \[^30\]. Here, we report data on depression and apathy of, twenty-one CKD patients with age ranging from 37-79 years and twenty-two age matched healthy controls. All patients were treated at the dialysis unit of the two participating tertiary care centres in Hannover and Halle. Controls were recruited in the regions close to the two participating hospitals. Exclusion criteria employed at the recruitment stage were: impaired uncorrected vision, a history of head trauma, neurological signs and symptoms, substance abuse disorder, or psychiatric conditions other than depressive or anxiety disorders. Inclusion criteria for the CKD patients were an end-stage renal failure (CKD stage 5) and a routinely dialyses treatment for at least one month.

All participants were tested twice within a 24-hour retest interval. CKD patients were tested at two time points, immediately before dialysis as well as 24 hours after dialysis to assess the potential effect of dialysis avoiding circadian changes. Tests were performed in a quiet room. Controls were tested in their...
Mood State

To assess persistent deteriorations in mood a questionnaire of a German health survey of Quality of Life was administered\textsuperscript{[15]}. This questionnaire asks for prevailing mood, mood state, life orientation, somatic complaints, and social support within a time period of the last four weeks. We used a short form of the questionnaire with 28 items in total. Each item was measured on a 5-point rating scale and recoded such that higher values indicate a better mood state. The sum score of all items was conducted to the statistical analysis. This score was reported as consistent (Cronbach alpha = 0.88) and reliable (r\textsubscript{v} = 0.70) by the authors\textsuperscript{[15]}.

Mood Changes

In order to measure short-term changes in mood we needed a method that is sensitive enough to detect subtle differences within a very narrow time interval (24h retest interval). The multi-dimensional state questionnaire is a standardized instrument which is available in two forms (A and B) and met our requirements of short retest intervals\textsuperscript{[16]}. Form A and B were developed as parallel version and absolutely comparable. We chose both forms for the purposes of a repeated measure in our pre-post design. Form A was administered at the pre-dialysis test session, form B at the post dialysis session. Each form consists of 12 5-point Likert scale items that were summarized into a sum score. The scale measures good momentary mood: a person scoring high on that scale is feeling well, satisfied, and joyful. Internal consistency of form A and B was reported as good (Cronbach alpha = 0.70-0.8). Retest reliability between form A and B was reported with r\textsubscript{v} = 0.8-0.9.

Statistics

First, BDI and AES scores were computed for each participant and compared with the cut-offs. Based on this decision CKD patients were assigned into three subgroups: patients without apathy and depression (CKD−), patients with apathy only (CKD+A), and patients with depression (CKD+D). Healthy controls who meet the apathy or depression criteria were excluded from further analyses. The control group and the three CKD subgroups form the independent variable. Second, descriptive statistics (group means, standard deviations, standard error of means, or frequencies)
were computed for each dependent variable. Hypotheses’ testing was performed as group mean testing and relies on one-way ANOVAs and orthogonal linear contrast in case of comparing healthy controls and CKD patients. Comparisons of CKD patients only rely on one-way non-parametric ANOVAs by Ranks (H test), because of low group numbers. The general level of significance was set to $p<0.05$. Measurements of effect size were Cohen’s $d$ for between-group comparisons and Hedges $g$ for pre-post comparisons. Both are comparable in its possible size. A general guideline for interpretation of effect sizes is small (0.3), moderate (0.5), and large (0.8). Statistical calculations were performed with SPSS 20 software.

**Results**

**Apathy and Depression in CKD**

Seven CKD patients were identified with clinical relevant symptoms of depression ($BDI \geq 15$). Clinically relevant symptoms of apathy were detected in eleven out of 21 CKD patients and one control person ($AES \geq 34$). The diagnosis of apathy overlapped with the diagnosis of depression in four CKD patients. Seven CKD patients did show neither depression nor apathy symptoms. Figure 1 shows the assignment of CKD patients to the subgroups CKD─, CKD+A, and CKD+D, respectively. Note that we combined depressed patients with and without apathy in the CKD+D group. CKD+A represents patients with apathy only, free of symptoms of depression. Two participants of the control group were identified with depression or apathy and excluded from further analyses, such that the control group contains 20 participants.

Table 1 illustrates the characteristics of the CKD subgroups and the control group. Patients and controls were comparable in formal education, but not in their state of employment. No significant differences were obtained in the mean dialysis vintage (length of time on dialysis in month) between the CKD subgroups. However, the range of the dialysis vintage was very wide in all three groups.

Nine of the CKD patients were under medications with psychopharmacological effect: antidepressant and anticonvulsant drugs were most frequently used in the CKD+D group. Sedatives and analgesics were more frequent in CKD with apathy further indicating the subtle complaints in this group of patients.

Apathy and depression symptoms were further characterized by means of an analysis of the BDI and AES subscales, respectively. Somatic and cognitive-emotional symptoms and the BDI sum score were significantly increased in CKD patients compared to healthy controls. CKD+D patients differed significantly to the CKD+A and the CKD─ patients in these scores. However, an average BDI score of 17.4 in CKD+D patients indicated no more than a mild depression. CKD+A and CKD─ showed small but no significant differences compared to healthy controls. The subscale suicidal thoughts could not differentiate the CKD groups.

Behavioural and cognitive-emotional symptoms of apathy and the AES sum score were significantly increased in the CK+D as well as in the CKD+D group compared to healthy controls, indicating that depression shares nearly all symptoms of apathy. CKD─ patients obtained an AES profile that was comparable to those of the control group.

**Mood State and Mood Changes**

Figure 2A shows results of the evaluation of the prevailing mood state in CKD patients and healthy controls by means of the Quality of Life questionnaire. Healthy controls obtained the highest score, which in general indicates a well and stable mood in this group. CKD─ and CKD+A patients together scored significantly below the control group ($t(19.3)=2.98$, $p=0.008$, $d=1.1$). Both CKD groups estimated their overall mood state similar. CKD+D patients answered significantly increased in the CK+D as well as in the CKD+D group compared to healthy controls, indicating that depression shares nearly all symptoms of apathy. CKD─ patients obtained an AES profile that was comparable to those of the control group.
Table 1. Key demographic data of healthy controls and the post hoc sub groups of kidney disease patients. Reported are means, standard deviation, ranges and frequencies. Group differences are tested on significance (p-values).

|                              | Controls | CKD− | CKD+A | CKD+D | P-values |
|------------------------------|----------|------|-------|-------|----------|
|                              | N=20     | N=7  | N=7   | N=7   |          |
| Mean age in yrs. (SD)        | 56.6 (12.7) [33-80] | 56.9 (18.3) | 57.3 (7.9) | 54.4 (2.8) | 0.925    |
| [range]                      |          | (37-79) | 48-68 | (51-59) |          |
| No. of females               | 13 (65%) | 2 (29%) | 1 (14%) | 6 (86%) | 0.155    |
| Employed                     | 11 (55%) | 3 (43%) | 0 (0%) | 0 (0%) | 0.001    |
| High degree of formal educ-  | 9 (45%)  | 4 (57%) | 0 (0%) | 2 (29%) | 0.275    |
| [ation]                      |          | (1-88) | 1-184 | (3-196) |          |
| Psychopharmacological        |          |        |       |       |          |
| medication                   |          |        |       |       |          |
| Antidepressant               | 0 (0%)   | 0 (0%) | 2 (29%) | 3 (43%) | 0.020    |
| Anticonvulsive               | 0 (0%)   | 1 (14%) | 0 (0%) | 2 (29%) | 0.079    |
| Sedative, analgesic          | 0 (0%)   | 0 (0%) | 3 (43%) | 1 (14%) | 0.040    |
| Symptoms of depression       |          |        |       |       |          |
| (BDI)                        |          |        |       |       |          |
| Somatic symptoms             | 3.5 (2.6) | 4.4 (2.1) | 4.4 (0.8) | 8.0 (2.2) | 0.005    |
| Cognitive-emotional symp-    | 0.4 (0.6) | 0.9 (1.1) | 0.7 (1.5) | 3.3 (1.6) | 0.001    |
| toms                         |          | (0.3) | (1.1) | (1.3) |          |
| Suicidal thoughts            | 0.1 (0.3) | 0.1 (0.4) | 0.1 (0.4) | 0.3 (0.5) | 0.433    |
| Sum score                    | 5.7 (3.5) | 7.6 (3.7) | 8.0 (2.5) | 17.4 (1.7) | <0.001   |
| Symptoms of apathy (AES)     |          |        |       |       |          |
| Behavioural symptoms         | 13.0 (2.8) | 13.4 (1.8) | 19.4 (2.1) | 18.9 (5.5) | <0.001   |
| Cognitive-emotional symp-    | 6.5 (1.2) | 6.6 (1.5) | 9.4 (1.1) | 8.4 (2.7) | 0.002    |
| toms                         |          | (1.7) | (1.4) | (1.9) |          |
| Sum score                    | 25.5 (4.5) | 26.0 (4.7) | 38.0 (3.8) | 36.1 (10.1) | <0.001   |

CKD−: without apathy and depression  CKD+A: with apathy only  CKD+D: with depression and probable apathy
†: ANOVA contrast controls vs. all CKD groups  ‡: non-parametric omnibus test CKD groups only
below all other groups. Group differences were tested against healthy controls (t(8.7)=5.5, p<0.001, d=2.6) and against a combined group of CKD and CKD+A (t (9.2)=3.57, p=0.006, d=1.8).

Next we tested changes in mood related to the dialysis treatment. Figure 2B shows group means of the momentary mood estimated immediately before a haemodialysis session (pre dialysis) and 24 hours after the treatment (post dialysis). Pre-test scores of all CKD sub groups were significantly lower than the pre-test scores of the control group (t(37)=4.13, p<0.001, d=1.3). After the dialysis session and the 24h retention interval CKD patients stated a significant higher mood score than CKD+A and CKD+D (t(14.7)=2.63, p=0.019, d=1.2). Their post-test score increased significantly compared to the pre-test result (t(6)=2.62, p= 0.039, r=0.185, d=1.3) and reached the level of the mood of healthy controls. Pre-post changes occurred neither in the control group nor in the other CKD sub groups.

**Discussion**

In this study we tested how three different groups of CKD patients responded on a measure of short-term mood after a single session of haemodialysis. First, our findings suggest a high rate of apathetic patients (approx. two-third) among the CKD population. Second, a dichotomous distinction between patients with and without clinical relevant depression led to a sub group with symptoms of apathy only. These apathetic CKD patients showed the behavioural and cognitive-emotional symptoms of apathy, but lacked the somatic and cognitive-emotional symptoms of a prevailing depression, which clearly shows that patients were able to differentiate apathy and depression symptoms by means of self-report scales. Depressed mood (cognitive-emotional symptoms) turned out to be the best discriminator between patients with and without a depression. Suicidal thoughts, which were also suggested by former studies[3], could not discriminate between CKD groups as well as between patients and healthy controls.

**Limitations**

Clearly, our sample size is small and not reliable to derive a prevalence rate in general. The study relied on CKD patients receiving haemodialysis treatment only. No conclusions can be thrown on CKD patients receiving other treatments like peritoneal dialysis, which is not limited to a 4-5 hour treatment thrice weekly but is usually done daily over many hours. Symptoms of depression were reported as less frequent and less severe in these patients[20, 21]. Furthermore, symptoms of apathy strongly overlap with symptoms accompanying a depression, such that all depressed patients scored high on the apathy scale. It seems that patients suffering from a depressive disorder discern their depressiveness also as apathy, when assessed with the AES. Suicidal thoughts could also not discriminate...
between depression and apathy. This is probably due to a methodological weakness of our subscale analysis where the dimension suicidal thoughts relies on one BDI item only.

To further explore apathy in CKD we focused on the differential effect of apathy and depression on the sustained mood state. CKDs’ quality of life was often reported as severely affected by an additional depression[^17]. Reduced quality of life expresses sustained depressed mood as the prevailing affective state with high complaints, low social integration and coping. We identified a large effect for depression on quality of life measures with depressed CKD patients scoring 2.6 standard deviations below healthy controls. It confirms the tremendous deterioration of the mood state that depressed CKD patients often discern, and it should be a strong concern to treat clinical relevant depressions in patients with renal failure. But also CKD patients without depression and apathy reported restricted quality of life compared to healthy controls. The difference is also large in terms of an effect size (Cohen’s d=1.8), and it seems that CKD patients without apathy symptoms responded equally to the Quality of Life measure compared to patients with apathy. We suggest that the primary somatic complaints accompanying the disease and the dialysis procedure are most likely responsible for the reduced quality of life in these patients. Physicians can meet that challenge with the medical treatment of the renal disease. If patients develop depressive disorders then subjective health complaints and a loss of social integration become more prominent in CKD patients’ daily life. To treat these secondary complaints a psychotherapeutic intervention seems to be recommended[^18].

Apathetic CKD patients did not turn out to be at a higher risk than patients without apathy to develop further deteriorations in their prevailing mood state. Hence, in the second part of our study we tried to evaluate this outcome in terms of short-term mood changes. The momentary mood was assessed immediately before a dialysis session and 24 hours later after approximately one day of recovery. Here apathetic CKD patients showed a pattern comparable to that observed in patients with a clinical relevant depression. We could not show a short-term improvement in mood that was associated with the dialysis treatment in the apathetic CKD patients. In CKD patients without apathy we could demonstrated this possible effect. The mood of patients without apathy and depression improved nearly to the level of healthy controls. The effect size (within-subject d=1.3) indicated a large effect on our short-term mood measure.

The latter observation after all indicated apathetic patients as restricted as depressed patients. We argue that apathetic CKD patients are on risk to develop depressions later in the disease process. The absence of a (previously perceived) brightening effect could also mean a loss of positive reinforcement. Loss of positive reinforcement could negatively influence patients’ compliance and is a main factor in the aetiology of a major depression[^19]. Further research is necessary to confirm such an assumption, because our study is small in numbers and restricted to a very short longitudinal observation interval. We could give only a first impression of the importance of the concept of apathy in patients with severe CKD.

**Conclusion**

Chronic kidney disease patients undergoing haemodialysis frequently show loss of motivation, cognitive impairments, and emotional distress without suffering from a depression. Apathy as a symptom of the renal disease seems to be attributable to this state. Patients with apathy are less impaired in quality of life than patients with depression, but lack a positive emotional reactivity to the dialyses treatment, which was observable in patients without apathy and depression. The clinical practice could consider apathy as a severe symptom in patients with end-stage renal failure. It is possible to discriminate between depression and apathy in those patients with the self-report questionnaires BDI and AES. Treating apathy in CKD could improve the adherence to the requirements of the dialysis treatment and omit the progression of the disease, probable cognitive impairments and an emotional distress.

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