# Depression in pediatric chronic kidney disease

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A thesis

Submitted in partial fulfillment of the

requirements of the degree of

Master of Public Health

University of Washington

2012

Committee:

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Program Authorized to Offer Degree:

Epidemiology

University of Washington

**Abstract**

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Objective: To determine the prevalence of depression in pediatric patients with moderate to severe chronic kidney disease (CKD) and to identify associated patient characteristics.

Methods: We performed a cross-sectional study to assess depression in patients aged 9-18 years with CKD stages III-V. Each patient completed the Child Depression Inventory-2 (CDI-2) and a parent completed the parent CDI-2. Criteria for the presence of depression were CDI-2 scores >64 or a prior diagnoses of depression currently being treated. Relative risks and 95% confidence intervals were calculated to determine the patient characteristics associated with depression.

Results: Thirty-one percent of patients (13/42) met the criteria for depression, 18% of those ≤12 years and 35% of those >12 years. After adjusting for age and gender, risk of depression was relatively lower for patients with disease for ≤3 years (RR .19, 95% CI: .03, 1.23) and for those with CKD stage IV (RR .24, 95% CI .06, 1.02) and CKD stage V (RR .20, 95% CI: .04, 1.05) when compared to those with CKD stage III. In comparison to pre-end stage renal disease (ESRD) patients there was a lower risk for those on dialysis (RR .45, 95% CI: .09, 2.30) and a greater risk for those with a functioning transplant (RR 2.4, 95% CI: .98, 5.9).

Conclusion: There is a high prevalence of depression in pediatric patients with CKD. Patients with a functioning transplant or with CKD stage III may be at a relatively greater risk of depression. Our results are limited by statistical uncertainty due to the small sample size.

## Introduction

Depression is one of the most common psychiatric disorders. The prevalence of depression in the adult primary care setting is 5-10%.[1] The prevalence of depression in children and adolescents ranges from 0.4% to 8.3%, with a higher prevalence reported in adolescents.[2,3] Depression predisposes to suicide, and in patients with chronic illness it is associated with poor access to or use of health care, poor nutritional status, poor medical adherence and modification of the immunologic and stress responses.[4-7]

Studies in pediatric patients with chronic illnesses have shown an increased prevalence of depression compared to healthy populations. [8,9] This is important since depression may affect the primary medical problem.[10] Depression in pediatric patients with diabetes was associated with negative diabetes related health outcomes, such as higher hemoglobin A1C values, less frequent blood glucose monitoring and higher degrees of diabetes related co-morbidities in a study by Hood et al.[4] Similar to children with diabetes, children with chronic kidney disease (CKD) suffer from an illness that has no known cure and that demands daily life-style modification. These children may feel isolated from their peers. They often suffer from growth retardation, delayed development of secondary sex characteristics, and those on dialysis may have multiple surgical scars, a disfiguring fistula or an arteriovenous shunt. Signs and symptoms of depression, such as fatigue, insomnia, anorexia, and psychomotor retardation, overlap with those of CKD, making it difficult to recognize depression in these patients.[9,11-14] There are few studies addressing the prevalence of depression in pediatric patients with CKD.[13,15] These studies are limited by small numbers of subjects, often do not distinguish depression, anxiety and adjustment disorders, and do not examine the effects of depression on associated co-morbidities and medical adherence.[4]

Studies in adults with CKD indicate that the prevalence of depression is between 20-40%.[16-20] For adult hemodialysis patients, major depression is associated with a three to four fold greater risk of death.[20-22,24] Likewise, recent studies demonstrated that CKD patients not receiving dialysis had a prevalence of major depression of 21% and were at an increased risk of poor outcomes independent of co-morbidities and kidney disease severity.[22] Treatment of depression in adult patients with CKD has been shown to positively affect quality of life.[23]

We conducted a cross-sectional study to determine the prevalence of depression in pediatric patients with moderate to severe CKD and to identify patient characteristics associated with depression in this group.

## Methods

### *Study design and sample*

This study included pediatric patients with chronic kidney disease stages III-V. This level of kidney disease includes all children with an estimated GFR <60 ml/min/1.73m$^2$, including those on dialysis and those with a renal transplant. Study subjects were recruited from the pediatric nephrology clinic at Seattle Children's Hospital, a tertiary care 250 bed pediatric hospital serving as the referral center for the states of Washington, Alaska, Montana and Idaho. All English or Spanish-speaking patients between the ages of 9-18 years with chronic kidney disease stages III-V were eligible. Study visits occurred between January 1, 2011 and February 29, 2012. The study was approved by the Institutional Review Board of Seattle Children's Hospital, and all subjects provided written assent if <18 years of age or written informed consent if 18 years of age. One parent of each subject provided written informed consent.

*Measurements of outcomes and variables*

Clinical and demographic data for each subject were collected from the medical record at the time of the study visit. Current depression status was assessed by the Child Depression Inventory-2 (CDI-2),[24] a self-rating tool used to measure depressive symptoms and validated in children ages 6-17 years.[25] The subject completed the child version of the CDI-2 and a parent completed the parent version of the CDI-2 as a proxy for the child. A diagnosis of depression was assigned based either on scores ascertained from the parent and child CDI-2 or on a prior diagnosis of depression currently being treated as reported in the medical chart. All CDI-2 scores were assigned a T-value based on general population norms. Scores obtained from the CDI-2 were quantified as a binary outcome, with a score >64 indicating symptoms consistent with a diagnosis of depression. The results from the parent CDI-2 were used to assess the presence of depression in subjects <13 years of age, and the results from the self CDI-2 were used in those ≥13 years of age. CDI-2 sub-scores were also measured (emotional problems, mood/physical symptoms, negative self-esteem, functional problems, ineffectiveness and interpersonal problems).

The following patient characteristics were analyzed as categorical measures: gender; age (<13 year or ≥13 years); age at time of diagnosis (<5 years or ≥5 years); time since diagnosis of CKD (<3 years or ≥3 years); renal replacement status (pre-end stage renal disease (ESRD), dialysis or functioning transplant); glomerular filtration rate (eGFR) (ml/min/1.73m^2) (estimated from the bedside Schwartz equation [26] for subjects <18 years and by the Modification of Diet in Renal Disease Study Group equation[27] for subjects=18 years and designated as GFR 30-59 (ml/min/1.73m^2) =CKD stage III, GFR 15-29 (ml/min/1.73m^2) =CKD stage IV and GFR <15 or on dialysis=CKD stage V); height z score (<0 and ≥0); and body mass index (BMI) z score ( <1.5 and ≥1.5). Z scores were used in the analysis to standardize measurements for

age and gender. A change of one unit in the z score equals one standard deviation above or below the mean value for age and gender.

*Statistical Analysis*

Analyses were performed with STATA 10.0. Relative risks and 95% confidence intervals were calculated to determine the associations between each characteristic and the presence of depression. All relative risks were adjusted for age and gender because both characteristics are known to be associated with depression in the general population. [2,3]

**Results**

Sixty-seven eligible patients from the nephrology clinic were identified and 42 patients were enrolled in the study. Reasons for eligible patient non-participation were related to conflict between available study appointments and patient's availability in Seattle (n=15) and lack of interest (n=10). Non-participants had a similar gender distribution, but were more likely than participants to be CKD stage III and more likely to be of adolescent age. The baseline characteristics of the participants are shown in Table 1. The majority of the patients were of adolescent age and, following the expected demographics of pediatric CKD, the majority of subjects were boys, diagnosed at a young age, and shorter than average height.

Thirteen (31%) of the subjects met the study criteria for the presence of depression, 10 based on the results from the CDI-2 and four on the basis of a previous diagnosis of depression and were currently being treated. (One of the four subjects with a previous diagnosis of depression was currently being treated and scored within the depressed range on the CDI-2, the other three scored in the normal range). Figure 1 displays the distribution of t scores in our study sample according to the classification provided by the CDI-2. The distributions of self CDI-2 scores in each measured subscale were similar to each other and to that of the overall depression score.

When comparing parent and self CDI-2 scores, four of the adolescents had scores indicative of depression on the self CDI-2 but not the parent CDI-2. Seven of the adolescents not categorized as depressed, because the self CDI-2 score was <65, had a parent CDI-2 score indicative of depression. None of the children <13 years old had a self CDI-2 score indicative of depression. Two of the children had a parent CDI-2 score indicative of depression and therefore were categorized as depressed.

Table 2 shows the percentage of depressed patients by patient characteristic with the adjusted relative risks and 95% confidence intervals. Although all of the 95% confidence intervals include the null, there are some notable trends in the data. The boys had a lower prevalence of depression than the girls (RR 0.42, 95% CI: 0.17, 1.02). When compared to adolescents, younger children had a lower prevalence of depression (RR 0.45, 95% CI: 0.09, 2.25). There was a suggestion of a lower risk of depression in those diagnosed with CKD after 5 years of age (RR 0.72, 95% CI: 0.25, 2.04) and a lower risk in patients whose time since initial diagnosis of CKD was < 3 years (RR 0.19, 95% CI: 0.03, 1.23). The patients on dialysis were less likely than the patients with pre-ESRD to be depressed (RR 0.45, 95% CI: 0.09, 2.30), and the patients with a functioning transplant were more likely than the pre-ESRD subjects to be depressed (RR 2.4, 95% CI: 0.98, 5.86). There was a negative association between depression and severity of CKD. Relative to the risk in patients with CKD stage III, the RR in patients with CKD stage IV was 0.24 (95% CI: 0.06, 1.02). The corresponding relative risk amongst patients with CKD stage V was 0.20 (95% CI: 0.04, 1.05). The data suggest that patients who are a shorter height than average have a higher likelihood of being depressed than those who are at or above average height (RR .45 95% CI: .13, 1.6). There did not appear to be an association between BMI and the prevalence of depression.

**Discussion**

Advances in the medical care of children with chronic kidney disease have increased the likelihood of their survival into adulthood. Consequently, the psychological well-being of these children increases in importance. The 31% overall prevalence of depression in our study indicates that depression is an issue for this population of children. Two prior studies have also addressed the prevalence of depression in pediatric CKD patients. One, by Berney-Martinet et al., assessed the lifetime prevalence of depression by clinical interview in 40 adolescent transplant patients and 20 adolescent pre-ESRD CKD patients.[15] They found an overall prevalence of 35%, comparable to the prevalence of depression in the adolescents in our study. The other study, by Bakr et al., assessed current depression by clinical interview, but included only pre-ESRD CKD patients (n=19) and hemodialysis patients (n=19).[13] They found a lower prevalence of overall depression (10.3%), all of which was in the hemodialysis group (26% depressed). The lower prevalence may be because most of the subjects in the Bakr study were of pre-adolescent age.

Although our study was not designed to determine if depression is more prevalent among pediatric CKD patients than in the general pediatric population, we suspect that this is true. The prevalence of depression that we found (18% in the child age group and 35% in the adolescent age group) was higher than the prevalence ranges cited in the literature for the general population of both age groups (0.4% to 8.3%).[23] Furthermore, we found that the mean self and parent CDI-2 scores in our study (means 55±11 and 58±12, respectively) were higher than those of the population on which the CDI-2 was validated (validated population means 50±10; for self CDI-2 t-test stat=3.0. p-value <.01; for parent CDI-2 t-test stat= 4.5, p-value<.01).[25]

To gain insight into the factors contributing to depression in CKD and to determine if there are groups of patients for whom depression is a more critical issue, we sought to identify factors associated with depression in our cohort. We found that the boys in our cohort were less likely to be depressed than the girls (21% versus 50%). This follows the expected epidemiology of depression, in that once adolescent age has been reached, females are more likely to be depressed than males.[2,28]

We also found that, even after adjusting for age, having a diagnosis of CKD for a longer time period was associated with a higher likelihood of depression. This could indicate that over time, the burden and stress of living with CKD increases and children with the disease are not adjusting to it. In contrast to our study, the study by Bakr et al. failed to show, without providing specific data regarding duration of disease, an association between duration of disease and depression.[13] The difference in findings between our study and the Bakr study may be related to the small sample size of the Bakr study (n=38) which makes it difficult to detect modest sized relationships, or because the median age of the Bakr study was younger than ours (12 years versus 14 years) and so may not have had enough older children in the study to adequately gage the impact of duration of diagnosis. Studies investigating depression in other pediatric chronic illness have also generally failed to find an association between depression and duration of illness.[29-32] One study of children with diabetes found that the highest risk of depression was during the first year following diagnosis. [29,31]

An unanticipated finding in this study was the inverse association of depression with severity of disease. We found more depression in the patients who were classified as CKD stage III than those classified as CKD stages IV and V. This finding suggests that depression may not be related primarily to the abnormal metabolic milieu of CKD patients, since those with worse kidney function would have more severe metabolic derangements. In an exploratory analysis we hypothesized that this finding may be reflective of the high percentage of transplant

patients in the CKD stage III group (50%), but excluding the transplant patients from the analysis did not change the magnitude of the association between severity of CKD and depression. We further investigated this inverse association by including in the analysis an adjustment for time since diagnosis of CKD. Inclusion of this adjustment yielded a slight attenuation of the association between stage of disease and depression when comparing CKD stage III to CKD stage IV (RR .24 versus .27 with time since diagnosis adjustment), thereby indicating that time since diagnosis may be a confounder in the association. An alternative explanation is that there are stronger influences on the presence of depression than kidney function. For instance, CKD stage III patients often do not have as frequent appointments as those with poorer kidney function, especially those on dialysis. This may actually limit the psychological support available to the CKD stage III patients in that they do not interact with their doctors, nutritionists or social workers as frequently as sicker patients and accordingly may feel more isolated. A study of depression in adult CKD patients also did not demonstrate an association between worsening kidney function and depression.[19]

Another finding in this study was the higher prevalence of depression in those with a transplant when compared to those on dialysis and those who were pre-ESRD. However, the study by Berney-Martinet et al., did not observe a higher prevalence of depression in the transplant patients and instead found that adolescents with a transplant and those with pre-ESRD had a similar frequency of depression (35%).[15] The small number of subjects in both studies limits any conclusions that can be drawn.

There are several limitations to this study. Some misclassification of depressed versus non-depressed individuals likely was introduced by the use of the CDI-2 as a basis for the case definition. The CDI-2, although validated in the general population, has not been validated in the pediatric chronic kidney disease population, and though based on the Diagnostic and Statistical Manual of Mental Disorders,[33] is not perfectly sensitive and specific relative to a

clinical diagnosis of depression. Despite these drawbacks, the CDI-2 is well validated in the general population and is easy to administer and interpret, and therefore served an important purpose by easily providing us with preliminary quantitative data regarding the burden of depression in this population. The cross-sectional design of the study also may have introduced misclassification since the depression inventories obtained information about depression only over the preceding two weeks. It is possible that the patient's status at the time point at which the outcome was assessed was not actually reflective of the patient's typical mental state. Another limitation to this study is the small number of subjects. This leads to a high level of statistical uncertainty for most of the associations we observed. Lastly, there may be a differential selection bias in the participants. Children who feel depressed may be less likely to agree to participate in the study because they are less active, sicker or less enthused about participation than children who are not depressed. Alternatively, some children may be more interested in participating if they feel depressed, since participation may promote diagnosis and subsequent treatment. The occurrence of both phenomena was suggested to us while undertaking this study, as some patients were eager to enroll because they saw participation as a means to finding help for what they considered to be depression, while others declined to participate because they felt that participation might make them feel more depressed.

There is evidence to suggest that depression plays an important role in the trajectory of chronic disease. In both pediatric chronic illness and in adult CKD, depression is associated with worse longterm outcomes.[15,20-22] The results of our study suggest that a high proportion of children with CKD are depressed and that those with the disease for more than 3 years, those with CKD stage III, and those with a transplant may be particularly susceptible. Depression may be one modifiable challenge that pediatric patients with CKD face, and by recognizing and treating it, the medical outcomes of these patients may improve.

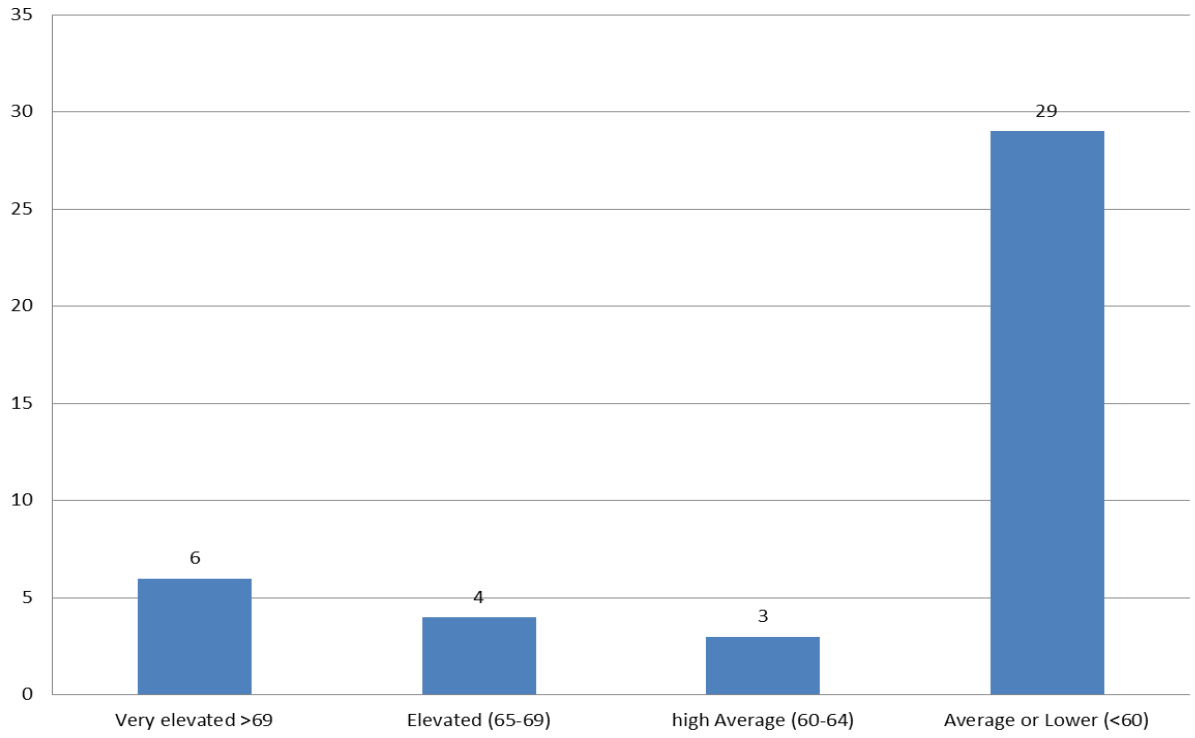
Table 1: Characteristics of subjects at time of study visit

| Characteristic | %(n) |
|---|---|
| Gender | |
| Female | 33 (14) |
| Male | 67 (28) |
| Age (years) | |
| 9-12 | 26 (11) |
| 13-18 | 74 (31) |
| Age at time of diagnosis of CKD (years) | |
| 0-5 | 55 (23) |
| 6-18 | 45 (19) |
| Time since diagnosis of CKD (years) | |
| 0-3 | 29 (12) |
| >3 | 71 (30) |
| Renal Replacement Status | |

| | |
|---|---|
| Pre-ESRD | 48 (20) |
| Dialysis | 33 (14) |
| Functioning Transplant | 19 (8) |
| CKD Stage | |
| CKD stage III (GFR[±] 30-59) | 33 (14) |
| CKD stage IV (GFR[±] 15-30) | 31 (13) |
| CKD stage V (GFR[±] <15 or dialysis) | 36 (15) |
| Height Z-score[*] | |
| <0 | 67 (28) |
| ≥0 | 31 (13) |
| BMI Z-score[*] | |
| <-1.5-1.5 | 83 (35) |
| >1.5 | 14 6) |

* A change of 1 unit in the Z-score equals one standard deviation above or below the mean value for age and gender
[±] Glomerular filtration rate

Figure 1: Percentage of Subjects with CDI Total Score in Various Ranges




*Scores ≥ 65 consistent with diagnosis of depression

Table 2: Correlates of depression in pediatric patients with CKD

| Characteristic | Depressed | | RR* | 95% CI |
|---|---|---|---|---|
| | n | % | | |
| Gender | | | | |
| Female | 7 | 50 | ---ref--- | ---ref--- |
| Male | 6 | 21 | .42 | .17, 1.02 |
| Age (years) | | | | |
| 9-12 | 2 | 18 | .45 | .09, 2.25 |
| 13-18 | 11 | 35 | ---ref--- | ---ref--- |
| Age at time of diagnosis of CKD (years) | | | | |
| 0-5 | 9 | 39 | ---ref--- | ---ref--- |
| 6-18 | 4 | 21 | .72 | .25, 2.04 |
| Time since diagnosis of CKD (years) | | | | |
| 0-3 | 1 | 8 | .19 | .03, 1.23 |
| >3 | 12 | 40 | ---ref--- | ---ref--- |

| | | | | |
|---|---|---|---|---|
| Renal Replacement Status | | | | |
| Pre-End stage renal disease | 5 | 25 | ---ref--- | ---ref--- |
| Dialysis | 2 | 15 | .45 | .09, 2.30 |
| Functioning Transplant | 6 | 75 | 2.4 | .98, 5.9 |
| CKD stage | | | | |
| CKD stage III (GFR[±] 30-59) | 9 | 64 | ---ref--- | ---ref--- |
| CKD stage IV (GFR[±] 15-30) | 2 | 15 | .24 | .06, 1.02 |
| CKD stage V (GFR [±] <15 or dialysis) | 2 | 13 | .20 | .04, 1.05 |
| Height z score | | | | |
| <0 | 10 | 36 | ---ref--- | ---ref--- |
| ≥0 | 2 | 15 | .45 | .13, 1.6 |
| BMI z score | | | | |
| <1.5 | 11 | 31 | ---ref--- | ---ref--- |
| ≥1.5 | 2 | 33 | .68 | .16, 2.8 |

* RR adjusted for age and sex
[±] Glomerular filtration rate

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