

**SLEEP QUALITY, DEPRESSION, AND QUALITY OF LIFE IN PATIENTS  
WITH CHRONIC KIDNEY DISEASE:  
A SINGLE CENTRE EXPERIENCE**

by

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## **ABSTRACT**

Background: Sleeping problems and depression are more common in patients with chronic kidney disease (CKD) than the general population. The primary objective of this cross-sectional study was to test factors associated with sleep disturbances, depression, and quality of life among patients with CKD.

Methods: We recruited patients with CKD who lived in the St. John's area from September 2012 to December 2012. The Pittsburgh Sleep Quality Index (PSQI), the Berlin Questionnaire (BQ), the Beck Depression Inventory (BDI), the Beck Depression Inventory Fast-Screen for Medical Patients (BDI-FS), and the Short Form 36 Quality of Life Health Survey Questions (SF-36) were administered to all participants. A chart review was performed for the patients' demographics, diagnoses, medication lists, and certain laboratory parameters—including blood glucose, hemoglobin, albumin, calcium, phosphate, parathyroid hormone, and estimated glomerular filtration rate (e-GFR). Logistic regression models were employed to estimate odds ratios (OR) with 95% confidence intervals (CI).

Results: The sample had a total of 303 patients (41% female and 99% Caucasian). One hundred and seventeen (39%) patients were labeled as poor sleepers with the PSQI, while 157 (51.8%) patients had high risk for sleep apnea in the study cohort. Physical component scores (PCS) and mental component scores (MCS) of the SF-36 questionnaire were significantly lower in the dialysis group when compared to the non-dialysis group.

A higher risk for impaired sleep was associated with being a female and on antidepressants and/or benzodiazepine or non-benzodiazepine hypnotic agents.

Conclusions: Sleep problems and depression are common in kidney patients. Women are more prone to sleeping problems than their male counter-parts. Furthermore, people who have low MCS scores are more prone to impaired sleep or vice versa.

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## **LIST OF ABBREVIATIONS AND SYMBOLS**

ACR: Albumin creatinine ratio

ACTH: Adrenocorticotrophic hormone

ADH: Anti diuretic hormone

BQ: The Berlin questionnaire

BDI: The Beck depression inventory

BDI-FS: The Beck depression inventory short form

BP: Bodily pain

CI: Confidence interval

CKD: Chronic kidney disease

CNS: Central nervous system

CPAP: Continuous positive airway pressure

CRH: Corticotrophin Releasing Hormone

E: Epinephrine

ECG: Electrocardiogram

eGFR: Estimated glomerular filtration rate

EEG: Electroencephalogram

EMG: Electromyogram

EOG: Electro-oculogram

GABA: Gamma Amino Butyric acid

GH: General health

HD: Hemodialysis

HPA: Hypothalamic-pituitary-adrenal

ICSD: International Classification of Sleep Disorders

IWG: Interdialytic weight gain

Log: Logarithmic transformation

MAP: Mean arterial pressure

MCS: Mental component summary

MDRD: Modification of diet in renal disease

mg: milligrams

MH: Mental health

min: minutes

ml: millilitres

mmol: millimoles

NE: Norepinephrine

NKF KDOQI: The National Kidney Foundation Kidney Disease Outcome Quality Initiative

NREM: Non rapid eye movement

OA: Obstructive apnea

OR: Odds ratio

OSA: Obstructive sleep apnea

PCS: Physical component summary

PD: Peritoneal dialysis

PP: Pulse pressure

PTH: Parathyroid hormone

PS: Parasympathetic

PSQI: Pittsburgh Sleep Quality Index

RDI: Respiratory disturbance index

RE: Role emotional

REM: Rapid eye movement

RP: Role physical

S: Sympathetic

SF: Social functioning

SF-36: Short Form 36 Quality of Life Health Survey Questions

SSRI: Serotonin receptor reuptake inhibitors

US: United States

VT: Vitality

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## **Chapter 1: INTRODUCTION**

### **1.1 The Overview**

Chronic kidney disease (CKD) is a global public health problem that is expected to affect a great number of people in coming years.<sup>1-3</sup> The condition is irreversible and related to shorter life expectancy.<sup>2,8</sup> Infectious agents, drug-related causes, and glomerulonephritis are among the most common causes for CKD in developing countries, while diabetes mellitus and vascular/hypertension related disorders are responsible for causing the vast majority of cases in developed countries.<sup>4-7</sup> Disease-specific treatment may be necessary in certain cases;<sup>8</sup> management usually relies on preserving the current kidney function.<sup>8,9</sup> When kidney function is diminished by about 90%, one of the renal replacement therapies needs to be employed. This may include dialysis or a kidney transplant.<sup>9</sup>

Sleeping problems and depression are more common in patients with kidney dysfunction.<sup>10-17</sup> The gold standard for the diagnosis of depression is a patient-centered, structured interview,<sup>11</sup> while sleep apnea requires polysomnography to make a definitive diagnosis.<sup>12</sup> These clinical conditions have been associated with adverse health outcomes.<sup>13</sup> Thus, it is important to diagnose and provide appropriate management in a timely manner.

Although not a substitute for the gold standard, questionnaires—widely available and accessible tools—are used before more detailed exams or diagnostic procedures are employed. The Pittsburgh Sleep Quality Index (PSQI)<sup>14</sup>, Short Form 36 Quality of Life

Health Survey Questions (SF-36)<sup>15</sup>, and Beck Depression Index (BDI)<sup>16</sup> were validated in CKD patients, and can be used for assessment of sleep quality, quality of life, and depression respectively. The Berlin Questionnaire (BQ)<sup>17</sup> was also validated for sleep apnea screening. The aforementioned tools do not pose any risk in their application, and are easily applied. Therefore, their use has been reported in numerous studies world-wide.

18,19,20,21,22

Screening tools are usually applied to high-risk populations for the associated condition, as mass screening may not be feasible. As a result, stratification of patients according to their risk status enables target screening, which decreases workload and unnecessary procedures. The determinants of sleep quality and depression in CKD patients have not been fully understood, although several predictors for both conditions have been well-established in the general population.<sup>23-28</sup> Identifying predictors for sleep quality are important since some of them may be modifiable, including blood glucose, blood pressure, obesity, and smoking.<sup>29-30</sup> Moreover, sleep apnea and depression might share the same causal pathway with renal disease progression, such as sympathetic nervous system activation.<sup>2</sup> Further, impaired sleep might lead to depression or vice versa.<sup>31</sup> High prevalence rates and lack of knowledge regarding the correlates of the entities in kidney patients necessitate exploring the field further. We expected to identify factors strongly associated with poor sleep quality in patients with various stages of renal failure.

## **1.2 The Literature Review**

A literature review was performed. The searches were performed using the following databases (from inception to the week 3 of February 2013): MEDLINE (via PubMed), EMBASE, The Cochrane Library, and Web of Science. The following key words with various combinations were included in the search: “sleep quality,” “sleep apnea,” “sleep-disordered breathing,” “depression,” “depressive disorder,” “quality of life,” “chronic kidney disease,” “dialysis,” “hemodialysis,” and “peritoneal dialysis”. The search covered prevalence, predictors, correlations, and management in both sleeping problems and depression in patients with CKD.

## **Chapter 2: BACKGROUND**

### **2.1 Definitions**

#### **2.1.1 The Definition of Chronic Kidney Disease and its Epidemiology**

##### **2.1.1.1 The Definition of Chronic Kidney Disease**

CKD is described as kidney damage caused by structural or functional abnormalities that persist for at least three months.<sup>3</sup> One of the most widely used and accepted tools for defining CKD from a functional perspective is estimated glomerular filtration rate (eGFR).<sup>3</sup> Different methods can be employed for this estimate, including the Modification of Diet in Renal Disease (MDRD) study equation<sup>32</sup> and the CKD-EPI equation.<sup>33</sup> An eGFR value of 90 ml/min/1.73 m<sup>2</sup> or lower is considered CKD.<sup>3,9</sup>

CKD can be also defined with normal eGFR levels if there are structural abnormalities such as kidney cysts or stones.<sup>3</sup> Another example would include the albumin: creatinine ratio (ACR) in a spot morning urine sample.<sup>34</sup> This measurement is based on the comparison of the ratio of urine albumin to creatinine in mg/mmol, which provides a proxy for 24-hour albumin excretion.<sup>34</sup> Urine ACR equal to or more than 3.5 mg/mmol for females and 2.5 mg/mmol for males signifies microalbuminuria and may indicate CKD, even in the presence of an eGFR > 90 ml/min/1.73 m<sup>2</sup>.<sup>9</sup>

CKD can be divided into 5 stages according to eGFR (please see table 2.1 for the list of five stages of CKD).<sup>9</sup> Stage 5 status may require dialysis treatment (stage 5D) or a kidney

transplant (stage 5T).<sup>9</sup> However, some of the stage 5 CKD patients may be conservatively managed.

**Table 2.1:** Stages of CKD according to eGFR<sup>3</sup>

Stages of CKD	eGFR, ml/min/1.73 m <sup>2</sup>
Stage 1	≥90
Stage 2	60–89
Stage 3	30–59
Stage 4	15–29
Stage 5	< 15

Abbreviations: eGFR: estimated Glomerular Filtration Rate; CKD: Chronic Kidney Disease.

Low GFR and the presence of persistent proteinuria have been independently associated with prognosis of CKD<sup>9</sup> and lower survival rates.<sup>35</sup> In this study, only eGFR was employed for defining reduced kidney function, due to the lack of ACR data.

### **2.1.1.2 Epidemiology of Chronic Kidney Disease**

#### **2.1.1.2.1 The Prevalence and Incidence of Chronic Kidney Disease**

CKD is a growing concern around the world, and according to a number of reports, the prevalence of the disease is increasing.<sup>3</sup> Although the incidence and prevalence of CKD exhibit large variations between countries, approximately 8–16% of people are thought to be afflicted by CKD worldwide.<sup>7</sup> North America is one of the regions in the world with a high number of cases with CKD. The prevalence of CKD among the adult population has

been indicated as over 10% in the United States (US), according to recent reports.<sup>3,36</sup> However, the rate of CKD, between 2005 and 2010, was 6.3% when defined by eGFR, and 9.2% when defined by ACR, according to the United States Renal Data System report in 2012.<sup>37</sup> A 1.7% increase in the rates of CKD between the periods of 1988—1994 and 2005—2010 has been reported.<sup>37</sup> According to recent data, a total of 25 million people have CKD and 500,000 need some kind of dialysis therapy or a kidney transplant in the US.<sup>38</sup>

Canada is another country with high prevalence rates of CKD. A total of 38,000 Canadians had stage 5 CKD in 2009, according to the Canadian Organ Replacement Registry Report, and 59% (22,300) of stage 5 CKD patients were on dialysis treatment in the same year.<sup>39</sup> The number of patients with stage 5 CKD reached 40,385, as reported by the Canadian Organ Replacement Registry Report in 2011. The incidence of stage 5 CKD in the same year was 5489 and 159.2 rate per million people.<sup>40</sup> The prevalence rate for the same time period was 11,712 rate per million people in Canada.<sup>40</sup> Newfoundland and Labrador is one of the provinces with a high degree of disease burden.<sup>40</sup> In 2011, there were 141 incident cases of end-stage renal disease in the province, yielding an incident rate of 276.2 per million.<sup>40</sup>

In addition to North America, other parts of the world have been inflicted with the CKD epidemic. The prevalence of age-standardized CKD in the adult population in England from stages 3 through 5 was indicated as approximately 8.5%.<sup>41,42</sup> According to the United Kingdom Renal Registry Reports, a total of 41,776 adult patients with a prevalence of 694 per million population were on a renal replacement treatment in 2005.<sup>43</sup>

In 2008, the point prevalence was 756 rate per million people (a total of 58,287) for kidney failure while the incidence rate was 188 including pediatric patient population, according to the Turkish Registry Reports.<sup>44</sup>

Prevalence rates change dramatically according to the definition of CKD, to the methods for collecting data, and to the characteristics of the study population. As a result, it might be difficult to compare the frequency of the disease from different jurisdictions without a standardized approach. In a large community-dwelling elderly cohort report by Hemmelgarn et al., the prevalence rate of CKD was 35.4%.<sup>24</sup> In another report from the US, 7% prevalence was indicated using the Cockcroft-Gault formula.<sup>45</sup>

#### **2.1.1.2.2 Causes of Chronic Kidney Disease**

Renal registries fair better from an underlying diagnosis perspective as “the most possible cause for CKD” is one of the categories of the reports. These can thus serve as valuable data sources nationwide and enable comparisons between jurisdictions. The most common causes of CKD include glomerulonephritis, diabetes mellitus, renal vascular disease, polycystic kidney disease, drug-induced causes, pyelonephritis, and unknown causes.<sup>40,46</sup> The most frequent cause of CKD in developed countries is diabetes mellitus, while infectious diseases, drug-related conditions, and glomerulonephritis are held responsible for the majority of cases in developing countries.<sup>4-7</sup> Of all prevalent patients in Canada in 2011, the diagnosis most responsible for kidney failure was reported as diabetes mellitus (26%), followed by glomerulonephritis (22%) in the stage 5 CKD patient population.<sup>40</sup>

### **2.1.1.2.3 Risk Factors for Chronic Kidney Disease**

Hypertension, diabetes, and obesity are risk factors for CKD development.<sup>7</sup> A total of approximately 1.5 billion adults around the world are expected to have hypertension by 2025.<sup>47</sup> The prevalence of diabetes was 6.4% in 2010, and is expected to increase about 1.3% by 2030 worldwide.<sup>48</sup> Obesity has been associated with a higher risk for CKD development and/or progression, excluding the dialysis patient population.<sup>49</sup> The number of overweight people has been increasing.<sup>50</sup> As a result of the rise in the number of patients with hypertension, diabetes, and obesity, more people could be at risk for CKD development in the future.

### **2.1.1.2.4 Survival and Associated Factors in Chronic Kidney Disease**

CKD has been correlated with increased mortality rates, and cardiovascular causes have been indicated as the leading cause of death.<sup>51,52</sup> Age and primary diagnosis have been associated with prognosis in CKD patients.<sup>40</sup> While age has been negatively correlated with survival, gender has not been indicated to be of significant influence on survival.<sup>40</sup> Renal vascular disease and diabetes were shown to be related to the lowest five-year survival rates.<sup>40</sup>

Comorbid conditions such as anemia, abnormal phosphate and uric acid levels, vitamin D deficiency, cardiovascular disease, congestive heart failure, and diabetes were also negatively correlated to survival in CKD patients.<sup>52</sup> Anemia has been associated with increased cardiovascular disease and death in a large elderly study cohort.<sup>53</sup> Hyperphosphatemia has been correlated with progression of chronic kidney disease and

increased mortality.<sup>54</sup> PD patients with high uric acid levels in a retrospective study indicated lower survival rates.<sup>55</sup> It was suggested by Anand et al. that vitamin D deficiency might lead to increased mortality in dialysis patients.<sup>56</sup> Similarly, it was indicated that oral vitamin D supplementation was associated with lower mortality in peritoneal dialysis (PD) patients.<sup>57</sup> The presence of vascular disease has been associated with lower survival rates in CKD patients.<sup>58</sup>

#### **2.1.1.2.5 Costs Associated with Chronic Kidney Disease**

Although the health effects of CKD have been studied thoroughly, few studies analyzed the economic burden associated with the disease. It was shown that cumulative costs for inpatient visits, outpatient visits, and prescriptions were significantly higher in CKD patients, when compared to the non-CKD group in a large-scale case control design.<sup>59</sup>

Total costs for treating dialysis patients have been rising. The cost has been reported as approximately \$40 billion US in 2009.<sup>60</sup> The reimbursement for each hospital hemodialysis session in the US was reported as \$689 US, while the amount was \$745 US per session in Ontario, Canada.<sup>61</sup> Reports also indicate that direct medical costs constitute 70-80% of the total costs.<sup>61</sup> A total of 30 hemodialysis patients were included in a prospective study with a six-month follow-up, and 76% of the total costs were attributed to direct medical and non-medical costs in India.<sup>62</sup> Parallel to these findings, direct medical costs were reported as 81%, and the mean total cost per hemodialysis session was \$297 US.<sup>63</sup> Health expenditures in those with non-dialysis CKD as compared to the

dialysis population are less measurable. Strategies to improve allocation of limited health resources without compromising patients' health and wellbeing require further research.

#### **2.1.1.2.6 Quality of Life in Chronic Kidney Disease**

Measurement of physical functioning is recommended, using SF-36 twice a year for dialysis patients.<sup>64</sup> Quality of life was shown to be lower in dialysis patients when compared to the general population.<sup>65</sup> It was also indicated that CKD contributes to poor quality of life and productivity losses.<sup>54,59</sup> Regular assessment, encouragement for physical activity, and management of modifiable factors are recommended to increase physical and mental wellbeing of CKD patients.<sup>59,64</sup>

#### **2.1.1.2.7 The Management of Chronic Kidney Disease**

Since CKD affects all organ systems, the management of the condition requires a systematic approach and detailed considerations for preserving kidney functions and preventing extra-renal complications.<sup>9</sup> Measurable care outcomes are considered to be cornerstones in CKD management, such as blood pressure, hemoglobin A1C, cholesterol, proteinuria, anemia, markers of bone and mineral metabolism, and dialysis adequacy for small solute clearance. However, these markers' association with patient-oriented outcomes is controversial.<sup>7,9</sup> Emerging issues such as sleeping problems and depression have added new components to the standard care for kidney patients.<sup>64</sup> Nevertheless, the most effective approach to prevent or even reverse progressive loss of kidney function is yet to be discovered.

A dialysis treatment or a kidney transplant needs to be started when patients reach the kidney failure stage. The vast majority of patients with kidney failure in the US prefer hemodialysis (HD).<sup>66</sup> According to a recent report, the initial treatment of choice for dialysis treatment was HD in approximately 80% of patients in Canada.<sup>40</sup> The most preferred choice as the initial dialysis treatment was HD in Newfoundland (93%), followed by New Brunswick (87%).<sup>40</sup> PD, as the initial treatment of choice for dialysis, was about 16% Canada-wide.<sup>40</sup> Newfoundland has the lowest provincial rate (7.2%) for incident PD patients.<sup>40</sup> In only 4% of kidney failure patients Canada-wide, pre-emptive transplantation was the treatment of choice in the same year.<sup>40</sup>

Arterial hypertension frequency in the CKD population has been shown to be high, with prevalence rates of 60%—82%.<sup>67-69</sup> In addition to salt and water retention,<sup>70,71</sup> increased sympathetic tone plays a major role in many cases and restoring the balance might be difficult.<sup>72,73</sup> Adequate blood pressure control prevents several life-threatening complications and increases survival in CKD patients.<sup>7</sup> It is worthwhile to test the association between blood pressure measurements and sleep quality, as imbalanced autonomic nervous system function promotes and provokes both conditions.

The focus of this thesis is on problems that may be more commonly seen in CKD patients. Some of the relevant information about sleeping problems, depression, and quality of life in the general population is provided in the following chapters. The prevalence, risk factors, and health outcomes of these conditions in those with CKD will also be addressed.

## **2.1.2 The Definition of Disordered Sleep and its Epidemiology**

### **2.1.2.1 An Overview of Sleep**

Sleep has been an area of interest for many researchers. People spend approximately one third of their lifetime sleeping. Sleep is not a unified entity, but has different stages.<sup>60</sup> Rechtschaffen and Kales first identified and scored sleep stages in 1967.<sup>60</sup> According to this classification system, sleep consists of alternating rapid eye movement (REM) and non-rapid eye movement (NREM) stages, which further divides into four stages.<sup>74,75</sup> REM is composed of tonic REM, which is characterized by absence of muscle tone and eye movement, and phasic REM, which is characterized by muscle twitches and rapid eye movement.<sup>76,77</sup> Please see appendix D for the diagram.

According to the Rechtschaffen and Kales classification, an epoch is a basic unit in polysomnography and represents a stage of sleep.<sup>75</sup> A scoring system is developed based on electroencephalogram (EEG), electro-oculogram (EOG), and chin electromyogram (EMG) tracings.<sup>75</sup> Due to subjectivity associated with tracing interpretation, the evaluation system raised some concerns and required further improvement.<sup>78</sup>

An updated scoring system was provided by the American Academy of Sleep Medicine in 2007.<sup>79</sup> According to this manual, sleep stages are defined as REM and NREM. NREM is divided itself into stages 1, 2, 3, and 4.<sup>79</sup> Moser et al. tested the degree of agreement between the two sleep-classification systems.<sup>78</sup> It was indicated that the percentage of total sleep time spent in stage 1, stage 2, and stage 3 was significantly different between the two classification systems.<sup>78</sup> However, the total sleep time, sleep latency, and sleep

efficiency did not differ.<sup>78</sup> Overall, the recent classification system decreased subjectivity in scoring, and as a result, it is preferred over the previous version.

After the discovery of sleep stages, changes in the autonomic nervous system activity during different stages of sleep have also been studied. NREM sleep is associated with increased parasympathetic and decreased sympathetic activity.<sup>80</sup> The outcome of this change is a drop in heart rate, blood pressure, and cardiac output.<sup>80</sup> Nocturnal dipping is described as a 10%—20% drop of systolic blood pressure and requires normal vagal activity and cardiovascular relaxation.<sup>81</sup> In many patients with kidney disease, due to an overactive sympathetic nervous system, nocturnal dipping is lost.<sup>82</sup> Thus, those patients are called non-dippers and exhibit a blood pressure drop of less than 10% during sleep.<sup>83,84</sup>

Further deterioration can be observed in reverse dippers, who have severely impaired autonomic function, with high blood pressure during sleep and eventually during wakefulness.<sup>77</sup> As a result of changes in parasympathetic and sympathetic activity, an increase in blood pressure by 5% is also expected in REM sleep.<sup>77</sup> Aside from the cardiovascular system, kidneys also experience some changes during sleep such as a decrease in GFR, renal blood flow, and the excretion of sodium and calcium; this is coupled with an increase in tubular water reabsorption and antidiuretic hormone (ADH) secretion.<sup>77</sup> Plasma renin activity and aldosterone also fluctuate during different stages of sleep.<sup>77</sup>

Different classifications for sleep disorders are available, including the International Classification of Sleep Disorders (ICSD)<sup>85</sup> and the Diagnostic Classification of Sleep and Arousal Disorders.<sup>86</sup> The ICSD classification provides an axial system for sleep disorders.<sup>85</sup> Axis A includes primary sleep diagnoses that are further divided into four categories: dyssomnia, including insomnia and excessive sleepiness; parasomnia; medical or psychiatric sleep disorders; and proposed sleep disorders.<sup>85</sup> Axis B contains diagnostic tools including tests and procedures, such as all-night polysomnography and multiple sleep latency tests.<sup>85</sup> Axis C lists medical or psychiatric disorders that are not primary sleep disturbances; recurrent depression and hypertension are classified under this category.<sup>85</sup> According to the Diagnostic Classification of Sleep and Arousal Disorders classification system, sleep disturbances can be divided into four major categories: disorders of initiating and maintaining sleep, disorders of excessive somnolence, disorders of sleep-wake cycle, and parasomnias.<sup>86</sup> Insomnia and sleep apnea are among the most common diseases that lead to poor sleep quality.<sup>87</sup>

#### **2.1.2.2 Insomnia**

The ICSD defines insomnia as “having difficulty in falling to sleep or maintaining sleep associated with severe daytime impairment”.<sup>88</sup> The condition can be primary or secondary to pre-existing psychological diseases, especially mood and anxiety disorders.<sup>88</sup> The duration, frequency, and severity of the disease can differ.<sup>88</sup> According to the ICSD classification system, there are eleven types of insomnia including paradoxical, idiopathic, and adjustment insomnia.<sup>88</sup> In selected cases, a sleep study can be ordered for a definitive diagnosis, although it is costly and cumbersome.<sup>79</sup> There are several

questionnaires that indicate sleep quality, such as the PSQI.<sup>14</sup> The measurement section includes detailed information related to measurement and assessment of sleep quality.

The prevalence for chronic insomnia is about 10% in the general US population.<sup>89,90</sup> Female gender, low education, and low income are some of the risk factors for insomnia.<sup>23,24</sup> Insomnia has been associated with lower quality of life and comorbid conditions, such as depression and anxiety disorders.<sup>91,92</sup>

The association between sleep disturbances and shifted circadian rhythm of blood pressure has also been investigated. One hundred and thirty-three newly diagnosed hypertensive patients were included in the study, and sleep quality was assessed with the PSQI.<sup>93</sup> An ambulatory blood pressure monitoring system was also employed.<sup>93</sup> The PSQI global score was significantly elevated in non-dippers. Further, each component of the PSQI was also found to be elevated in non-dippers. As a result, it was concluded that the PSQI score was a predictor for non-dipping status (OR: 0.84,  $p < 0.004$ ).<sup>93</sup> Similarly, it was also shown that the PSQI global score was negatively correlated with night-time systolic and diastolic blood pressure readings ( $r$ : -0.46 and  $r$ : -0.42, respectively). Non-dippers scored higher in the PSQI.<sup>94</sup>

### **2.1.2.3 Sleep Apnea**

Sleep disordered breathing, also called sleep apnea, consists of a wide spectrum of diseases, from snoring to severe hypoxemia, that lead to consequent pathophysiological changes in different organ systems.<sup>95</sup> The disease is characterized by transient cessation of breathing during sleep and can be with or without a compromised respiratory drive.<sup>95</sup>

Combination of sleep-disrupted breathing and excessive day-time sleepiness is called sleep apnea syndrome.<sup>95</sup>

The terminology for sleep apnea facilitates clarity for diagnostic criteria and management, and some of the definitions are provided in the following pages. Hypopnea is described as a drop in airflow of at least 50% for at least 10 seconds and with a minimal oxygen desaturation of 3%.<sup>95</sup> A drop in airflow of at least 90% for at least 10 seconds is considered apnea.<sup>95</sup> The severity of the disease is defined by an apnea / hypopnea index, which is calculated by the total events per sleep divided by the total sleep time in hours.<sup>95</sup> Thus, the hourly rate of apnea and hypopnea is calculated. If the number of events is between 5 and 15 per hour, it is called mild; if the number exceeds 30 per hour, it is classified as severe sleep apnea.<sup>95</sup>

According to the method for diagnosis, the prevalence of sleep apnea varies between 2% and 26 % in the general population.<sup>25,29,96-99</sup> Young et al. studied the prevalence of sleep-related breathing disorders in the middle-aged population with a sleep study (n: 602). It was shown that the prevalence of sleep apnea was 2% in women and 4% in men.<sup>29</sup> Another population-based study in Spain indicated that 2.2% of men and 0.8% of women were diagnosed with sleep apnea, which was based on a questionnaire and nocturnal home oximetry.<sup>97</sup> Parallel to these findings, in a large number of participants it was indicated that 1.9% of the respondents were diagnosed with sleep apnea.<sup>98</sup> In another report, a questionnaire and home monitoring of respiratory disturbance index (RDI) were used for sleep apnea diagnosis. Of the 441 patients in this study, 17.9% of the participants met criteria for sleep apnea.<sup>99</sup> 26% prevalence was indicated when the Berlin

Questionnaire (BQ) was employed as the screening tool, and 57% of overweight participants were at high risk for sleep apnea.<sup>96</sup>

Age, male gender, and obesity are the risk factors for developing sleep apnea in the general population.<sup>29</sup> In addition, non-traditional risk factors, such as HbA1C, diabetes mellitus, smoking, depression, and anxiety have also been investigated for sleep apnea risk in the general population. Priou et al. studied 1599 non-diabetic patients to test the association between HbA1C and sleep apnea.<sup>100</sup> Obstructive sleep apnea (OSA) severity and nocturnal hypoxemia were associated with HbA1C after adjustments were made for traditional risk factors, including age, sex, and body mass index (BMI).<sup>100</sup> Patients with moderate and severe OSA had a higher chance of having HbA1C > 6% (OR: 1.8, 95% CI: 1.19–2.72 for moderate OSA and OR: 2.02, 95% CI: 1.31–3.14 for severe OSA).<sup>100</sup> It was also reported that diabetes mellitus has been associated with sleep apnea.<sup>101,102</sup> Furthermore, it was reported that current smokers were at risk for moderate sleep apnea, when compared to non-smokers (OR: 4.44).<sup>30</sup> The study included a total of 811 adults, and a sleep study was performed for diagnosis.<sup>30</sup> This finding was supported by a recent report that included 57 patients with sleep apnea.<sup>103</sup> Duration of smoking was associated with the severity of sleep apnea and some structural uvular abnormalities in the tissue specimens.<sup>103</sup> Depression was associated with a 2.5 times higher risk for sleep apnea in the general population.<sup>102</sup> Lastly, a link between schizophrenia, anxiety, and OSA has also been suggested.<sup>104</sup>

In regards to the negative health outcomes, sleep apnea has been associated with increased risk for stroke,<sup>105</sup> hypertension,<sup>106</sup> inadequate diabetes control,<sup>107</sup> cardiovascular

events,<sup>108,109</sup> and pulmonary hypertension.<sup>110,111</sup> An overactive sympathetic tone in sleep apnea has been implicated for poorly controlled diabetes and hypertension.<sup>111</sup> An increased cardiovascular event risk in sleep apnea has also been related to sympathetic activation and endothelial dysfunction.<sup>13</sup>

OSA has been associated with cardiovascular mortality and morbidity in the general population. Marin et al. studied 1889 normotensive patients with and without OSA for hypertension development with a follow-up period of up to 17 years.<sup>112</sup> Those with an OSA diagnosis were further classified as (continuous positive airway pressure) CPAP recommended and CPAP not recommended.<sup>112</sup> Patients who did not adhere to CPAP treatment exhibited higher risk for developing hypertension (HR: 1.78, 95% CI: 1.23–2.58) when compared to their adherent counterparts (HR: 0.71, 95% CI: 0.53–0.94), after adjustments were made for baseline covariates.<sup>112</sup> It was concluded that CPAP treatment lowered the number of incident cases with hypertension.<sup>112</sup> In line with these findings, another community-based study supports the evidence regarding the correlation between OSA and hypertension development.<sup>99</sup> In a study cohort of 441 people, snorers and non-snorers were compared in terms of hypertension and coronary artery disease.<sup>99</sup> It was reported that patients with OSA had approximately a four times increased prevalence for high blood pressure (OR: 3.8, 95% CI: 1.9–7.5 for hypertension and OR: 3.5, 95% CI: 1.2–10 for coronary artery disease) in unadjusted models.<sup>99</sup> This finding was previously supported in three studies.<sup>13,113,114</sup>

In addition to long-term negative health outcomes, sleep apnea has been linked to a higher likelihood of daytime sleepiness, which is a known risk factor for accidents.<sup>98,115</sup>

Patients with sleep apnea were tested with a computer-simulated road test and indicated higher likelihood for accidents as compared to control subjects.<sup>116</sup> The fear of losing one's driver's license might pose a barrier to reporting the symptoms of sleep apnea. As a result, sleep apnea might be under-diagnosed.

There have been several theories to explain the underlying mechanisms of sleep apnea (please see appendix B). First of all, autonomic system dysfunction is held responsible for the disease causation and severity. The exacerbated sympathetic tone and consequent activation of the renin angiotensin aldosterone system play a major role in the disease process.<sup>117,118</sup> Structural abnormalities in the upper airway system are other considerations, and can be congenital or acquired.<sup>119</sup> Acquired causes include obstruction of the airway as a result of excessive fat tissue or fluid. As a result, obesity and hypervolemic states such as congestive heart failure<sup>120</sup> and CKD<sup>121</sup> have been associated with the syndrome. An abnormal muscle function in the upper respiratory tract<sup>119</sup> and possible fluid shift to the upper part of the body due to the recumbent position are considered other possible contributors.<sup>122-124</sup>

Tailored interventions for the management of sleep apnea, depending on the clinical condition and patients' preferences, are possible. Underlying conditions, which may contribute to sleep apnea, such as hypothyroidism and acromegaly, should be considered and/or treated as the initial step.<sup>125-127</sup> CPAP treatment, upper airway surgeries, and oral appliances are among different therapeutic choices<sup>125</sup>. Weight loss can be beneficial to those who are overweight.<sup>125</sup> Supplemental oxygen and positional therapy (elevated head posture, supine posture, and specifically designed pillows) may be used in certain cases

without a proven survival benefit.<sup>125</sup> Serotonin has mixed effects in terms of activating or inhibiting upper airway dilator activity and central drive.<sup>125,128</sup> Paroxetine and Fluoxetine are two of the selective serotonin reuptake inhibitors (SSRI) that have been shown to significantly decrease apnea hypopnea index.<sup>128,129</sup> Moreover, REM sleep suppressant therapy includes SSRIs, such as Fluoxetine and Paroxetine, and tricyclic antidepressants, such as Protriptyline and Clonidine.<sup>125</sup> This therapy can be administered to those with REM related OSA.<sup>128</sup> Methylxanthines, including Aminophylline and Theophylline might also be beneficial in central sleep apnea.<sup>130,131</sup> All in all, CPAP is the only treatment option that lowers the risk of mortality.<sup>132,133</sup> It has been also indicated that CPAP treatment provides significant attenuation in daytime sympathetic activity.<sup>134,135</sup>

### **2.1.3 The Definition of Depression and its Epidemiology**

#### **2.1.3.1 An Overview of Depression**

The Diagnostic and Statistical Manual for Mental Disorders IV is a widely accepted classification system for mental disorders.<sup>136</sup> It provides a classification system that employs five axes.<sup>136</sup> Axis 1 includes clinical disorders, including major endogenous depression, while Axis 2 represents personality disorders.<sup>136</sup> Axes 3, 4 and 5 encompass all physical, social, and environmental aspects and determinants for mental health.<sup>136</sup> Endogenous depression is included in Axis 1 with other major psychiatric disorders.

The definition of depression is as follows:

a clinical syndrome lasting at least two weeks, during which  
the patient experiences either depressed mood or anhedonia

plus at least five of the following symptoms: (1) depressed mood most of the day, nearly every day; (2) markedly diminished interest or pleasure in most activities most of the day; (3) significant weight loss or gain or appetite disturbance; (4) insomnia or hypersomnia; (5) psychomotor agitation or retardation; (6) inappropriate guilt; (7) diminished ability to think or concentrate, or indecisiveness; or (8) recurring thoughts of death, including suicidal ideation.<sup>136</sup>

In the general population, the point prevalence of depression is 5-9% in women, and 2-3% in men.<sup>137</sup> Female gender, obesity, and socioeconomic status are risk factors for depressive disorder.<sup>25-28</sup> Poor physical health has also been associated with increased risk for depression.<sup>138</sup> In a large study cohort with different chronic diseases, it was reported that those with kidney failure and coronary artery disease were more prone to depression, when compared to those with rheumatic diseases, such as rheumatoid arthritis.<sup>10</sup> The prevalence of depression was also shown to be higher in CKD patients as compared to the general population.<sup>139</sup>

Recurrent depressive disorder has been associated with negative health outcomes including the development of hypertension, cardiovascular disease, stroke, diabetes mellitus, and lower survival rates.<sup>140</sup> Depressive disorder has been associated with lower survival rates in those with diabetes, coronary heart disease and congestive heart

failure.<sup>141-143</sup> Similarly, patients with kidney failure and depression were found to have lower survival rates.<sup>144</sup>

Neurochemical imbalance in the central nervous system is the root of the problem in depressive disorder.<sup>145</sup> The disease process involves several alterations in the brain and in the peripheral nervous system, including reduced serotonin and increased sympathetic tone.<sup>145,146</sup>

The sympathetic nervous system is governed by the hypothalamic-pituitary-adrenal (HPA) axis. Corticotrophin Releasing Hormone (CRH) is one of the substances that is released by the HPA axis and stimulates the secretion of adrenocorticotrophic hormone (ACTH).<sup>147</sup> The ACTH stimulates the adrenal cortex and medulla, and increases Epinephrine and Norepinephrine levels.<sup>147</sup> It was previously reported that CRH increased in depressive patients.<sup>147</sup> The volume of space occupied by CRH neurons was significantly larger in patients with mood disorders.<sup>148</sup>

The HPA is inhibited by Gamma Amino Butyric acid (GABA) and cortisol feedback. GABA is a neurotransmitter that exerts control over both depression and sleeping problems.<sup>149</sup> An increased secretion has been observed with hypnotic medications, and reduced levels are evident in patients with depression and sleep disturbances.<sup>150</sup> The principal synthetic enzymes for GABA are Glutamic acid decarboxylase (GAD) 65 and 67.<sup>149</sup> The density of GAD 65/67 was negatively correlated with the density of CRH neurons in a study that included post-mortem samples.<sup>149</sup> In a review, it was also

indicated that plasma, cerebrospinal fluid and cortical levels of GABA were lower in patients with depression.<sup>151</sup>

In addition to GABA, alpha 2 adrenoreceptors also have inhibitory effects on the HPA.<sup>152</sup> These receptors can be found in the central nervous system (CNS), and have been related to the central neurotransmitter receptor functions of Norepinephrine.<sup>152</sup> Yohimbine acts as a receptor antagonist for alpha 2 adrenoreceptors and through this action has been linked to reduced Norepinephrine turnover.<sup>152</sup> A reduced alpha 2 adrenoreceptor function might cause increased central sympathetic tone, as a result of increased Norepinephrine production.<sup>152</sup>

Norepinephrine is one of the neurotransmitters of the sympathetic nervous system and has also been implicated in the pathogenesis of depression.<sup>146</sup> High total serum levels of Norepinephrine have been found in patients with depressive disorder.<sup>146</sup> Similarly, Veith et al. studied Norepinephrine kinetics in depression and indicated high plasma Norepinephrine levels were present.<sup>153</sup> High plasma Norepinephrine levels and high neuronal uptake of Norepinephrine in the CNS were also found by previous studies.<sup>154</sup>

Overall, the underlying pathophysiology of major depression is complex, and involves several substances.<sup>152</sup> Due to a lack of the negative feedback of GABA and/or alpha 2 adrenergic systems, the HPA becomes overactive with elevated CRH levels.<sup>152</sup> CRH stimulates corticotrophs, and ACTH is secreted. As a result, a sympathovagal imbalance is established, contributing to the disease process.<sup>120,121</sup>

Pharmacotherapy, psychotherapy, and electroconvulsive therapy are the cornerstones of major depression treatment.<sup>137</sup> Tricyclic antidepressants; monoamine oxidase inhibitors; SSRI; serotonin and noradrenaline reuptake inhibitors; and selective norepinephrine reuptake inhibitors are the main groups of medications.<sup>155-157</sup> SSRIs are considered as the first-line agents in the vast majority of cases due to their reasonable safety profile.<sup>157</sup> Ketamine is a glutamatergic N-methyl-D-aspartate receptor antagonist and a newly emerging therapeutic choice for depressive disorder.<sup>155</sup>

## **2.2 Measurements**

### **2.2.1 The Gold Standard and Surrogates for Measuring Sleep Disturbances**

There are several tools to diagnose sleep disturbances. A complete history-taking and a thorough physical exam should be the initial step.<sup>12</sup> Questionnaires can be employed to measure day time sleepiness and risk for sleep apnea.<sup>17</sup> Subjective information about the patient's sleep pattern can also be obtained by sleep logs.<sup>158</sup> Actigraphy is a tool used to assess sleep latency, sleep efficiency, total sleep time, and the number of awakenings during sleep.<sup>159,160</sup> Computed tomography and magnetic resonance imaging are among diagnostic modalities that are used to visualize the upper respiratory system.<sup>160</sup> Polysomnography, portable or in-center, is the gold standard for diagnosing many sleep disorders.<sup>12,161</sup>

#### **2.2.1.1. The Gold Standard for Diagnosing Sleep Disturbances**

The recommended objective testing method to establish a definitive diagnosis for sleep disturbances is a center-based polysomnography or home testing with portable monitors,

as previously mentioned.<sup>12,162</sup> EEG, chin EMG, and EOG are recorded during the sleep study.<sup>79</sup> Each sleep epoch is scored individually, according to the recordings from EEG, EMG, and EOG.<sup>79</sup> As a result, all stages of sleep are described.<sup>163</sup> Apnea hypopnea index and RDI are recorded throughout sleep.<sup>79</sup> The diagnosis of sleep apnea is made when the number of obstructive events, including apnea and hypopnea, exceeds 15 events per hour.<sup>79</sup>

Although the gold standard for the diagnosis of sleep apnea is polysomnography,<sup>12,162</sup> this method is cumbersome and costly. A few questionnaires, such as the PSQI<sup>14</sup> and BQ<sup>17</sup>, are used to screen sleeping problems and to select cases for further evaluation. The PSQI<sup>14</sup> includes questions about falling to sleep and maintaining sleep<sup>14</sup> while the BQ<sup>17</sup> focuses more on sleep apnea.

### **2.2.1.2 Surrogates for Measuring Sleep Disturbances**

Self-reported questionnaires are commonly used to evaluate various aspects of sleep conditions in the adult population. The Insomnia Severity Index (ISI),<sup>164</sup> Sleep Disorders Questionnaire,<sup>165</sup> Athens Insomnia Scale Instrument,<sup>166</sup> Post-Sleep Questionnaire,<sup>167</sup> and PSQI are briefly described and discussed in this paper, although there are many other instruments. Those questionnaires, which are validated with established reliability, simple, and well-accepted, are preferred in different health care settings.

The ISI questions problems about sleeping in the last two weeks.<sup>164</sup> ISI is assessed based on a global score with an emphasis on loss of day-time functioning, rather than severity of insomnia.<sup>168</sup> Sleep onset latency, sleep duration, and sleep medication use are not covered

in the ISI.<sup>168</sup> The tool indicated a high internal consistency value in menopausal women (the Cronbach's alpha: 0.87).<sup>169</sup> The PSQI and ISI were tested for accuracy and the area under the receiver operator characteristic curve was 0.79 and 0.78 for the PSQI and ISI, respectively.<sup>168</sup> The values between 0.8 and 0.9 indicates good diagnostic accuracy, while 0.9 and above is considered excellent for diagnostic accuracy.<sup>170</sup> As a result, the PSQI and ISI have a good diagnostic accuracy.

The Sleep Disorders Questionnaire has 175 domains, with categories for sleep apnea, narcolepsy, periodic limb movements, and psychiatric sleep disorders.<sup>165</sup> The test underwent validation against clinical evaluation and polysomnography, and indicated considerable test-retest reliability (Spearman rho for sleep apnea: 0.84).<sup>165</sup> However, the tool does not indicate sleep quality.

The Athens Insomnia Scale Instrument questions about problems falling to sleep during the past month.<sup>166</sup> The tool was indicated a considerable internal consistency and test-retest reliability (the Cronbach's alpha: 0.9 and the correlation coefficient: 0.9) in the general population.<sup>166</sup> A cut-off of 6 indicated 93% sensitivity and 85% specificity in a large study cohort.<sup>171</sup> The tool has not been validated in the CKD population.

### **2.2.1.3 The Pittsburgh Sleep Quality Index**

The PSQI is an instrument used to screen sleep quality and disturbances during the previous month.<sup>14</sup> The questionnaire poses a total of 18 questions with a score range of 0 to 21. The tool has seven domains: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime

dysfunction over the last month.<sup>14</sup> A sum of the seven component scores produces a global score. Buysse et al. studied 148 patients to validate the PSQI against polysomnography.<sup>14</sup> The report showed that the domains of the PSQI was internally consistent and valid after an 18-month period of field testing.<sup>14</sup> Furthermore, a global score higher than five was associated with 89.6% sensitivity, and 86.5% specificity in defining sleep quality, when compared to polysomnography.<sup>14</sup> The tool indicated test-retest reliability, and internal consistency was high (Cronbach's alpha: 0.83).<sup>14,172</sup>

The PSQI has several advantages over other assessment tools for sleep quality. Firstly, the instrument questions the intermediate time frame between post-sleep inventories, questioning the previous night's sleep and survey-type questionnaires, which in turn question the previous year. The post-sleep inventory and post-sleep questionnaire evaluate a subject's previous night's sleep.<sup>167,173</sup> A sleep diary questions about the past week, whereas the ISI questions about sleeping problems in the last two weeks.<sup>164</sup> Survey-type questionnaires evaluate a one-year timeframe, which might pose a risk for recall bias.

A global score also enables the comparison between subjects and within subjects.<sup>14</sup> Lastly, seven components of the PSQI screen possible sleep-related issues throughout the day and night.<sup>14</sup> The PSQI was also shown to be applicable to different patient populations, such as the elderly,<sup>174</sup> those with panic disorder,<sup>175</sup> those with AIDS<sup>176</sup>, and those with CKD.<sup>177</sup>

#### **2.2.1.4 The Berlin Questionnaire**

As previously mentioned, polysomnography is considered the gold standard for the diagnosis of sleep apnea, but in itself it is somewhat cumbersome and costly to screen for the disorder in those at risk. The BQ is a self-administered instrument used to screen for sleep apnea.<sup>17</sup> The questionnaire has ten questions and three components.<sup>17</sup> The first component has five items that indicate the presence and frequency of snoring in addition to witnessed apnea during sleep.<sup>17</sup> The second component is associated with wake-time sleepiness and fatigue.<sup>17</sup> Finally, the last component includes high blood pressure and obesity, defined as a BMI > 30Kg/m<sup>2</sup>. In components one and two, a total score of at least 2 is required to be qualified as a positive result.<sup>17</sup> On the other hand, category three is considered positive in the presence of either a diagnosis of hypertension or obesity.<sup>17</sup> If only one component of the three is positive, this indicates a low risk for sleep apnea.<sup>17</sup> If two or more components are positive, this indicates a high risk for sleep apnea.<sup>17</sup> Thus, the outcome of the tool is classified as high risk or low risk.

Netzer et al. tested the validity of the BQ in identifying high risk patients for sleep apnea in primary care settings.<sup>17</sup> In this study, the gold standard was the RDI assessed by portable monitoring during sleep.<sup>17</sup> An oxygen desaturation index was also assessed.<sup>17</sup> Of the 744 participants, a total of 279 (37.5%) were identified as at high risk for sleep apnea by the BQ.<sup>17</sup> One hundred had polysomnography with the portable monitor: 69 high-risk and 31 low-risk patients. A positive response in category one was associated with the highest post-test probability (78%) for a respiratory disturbance event, while a positive result in category two was associated with the lowest post-test probability (63%).<sup>17</sup>

Overall, the psychometric performance of the BQ against the RDI was as follows: sensitivity 86%, specificity 77%.<sup>17</sup> The major weakness about this study is that not all participants underwent polysomnography, which might pose a risk for a selection bias. The Greek version of the BQ was also validated against polysomnography in the primary care setting with a sensitivity of 76% and a specificity of 40%.<sup>21</sup> In another study by Amra et al., the sensitivity and specificity were reported 84% and 61.5%, respectively.<sup>22</sup> To our knowledge, the BQ has not been validated in CKD patients.

## **2.2.2 The Gold Standard and Surrogates for Measuring Depression**

### **2.2.2.1 The Gold Standard for Measuring Depression**

The gold standard for diagnosing depressive disorders is the structured clinical interview, according to the diagnostic criteria stated in the National Institute of Health and Clinical Excellence guidelines.<sup>11</sup> The Hamilton Depression Rating Scale<sup>178</sup> is one such interview-based diagnostic tools and can be administered by appropriately trained health professionals. The Hamilton Depression Rating Scale was used for depression screening in dialysis patients and indicated 35%–38% of patients had depression.<sup>179,180</sup>

Although the structured clinical interview is the gold standard for diagnosis, several validated questionnaires may be used for screening purposes. The KDOQI guidelines recommended several psychometric testing instruments for depression and anxiety screening in dialysis patients.<sup>64</sup> The Beck Depression Inventory (BDI)<sup>3</sup>, Beck Depression Inventory Short Form Medical Patients (BDI-FS)<sup>181</sup>, and Cognitive Depression Index (CDI)<sup>182</sup> are recommended by the guideline as tools for depression screening in dialysis

patients.<sup>64</sup> The BDI is one of the widely applicable self-report instruments for evaluation of depression both in the general population and among CKD patients. The BDI-FS<sup>181</sup> is a short form of the BDI and serves the same purpose. The CDI was produced from the BDI by omitting six somatic complaints of depression.<sup>183</sup> The tool was tested in dialysis patients, and results indicated that sensitivity and specificity associated with the tool was similar to the BDI.<sup>183</sup> Thus, it was indicated that the CDI was not superior to the BDI.<sup>183</sup> Moreover, the guideline indicated that the CDI might overestimate depression rates in the dialysis population.<sup>69</sup> The BDI was validated in CKD patients as a recommended tool for depression screening;<sup>64</sup> therefore, it was employed in this study.

#### **2.2.2.2 Surrogates for Measuring Depression**

#### **2.2.2.3 The Beck Depression Inventory**

The BDI is used to measure severity of depression.<sup>16,184</sup> The BDI was developed based on attitudes and symptoms of depressed patients that were represented in 21 categories. The tool was validated against the structured clinical interview with a high degree of reliability and validity in the general population.<sup>184</sup> Later on, the instrument was also validated for the dialysis population with a score cut-off of 16.<sup>185,186</sup> A total of 62 dialysis patients were studied to validate the inventory, which was shown to have 91% sensitivity and 86% specificity by Watnick and others.<sup>185</sup>

The standard version of the BDI has 21 questions, and each question is scored on a 4-point scale (0-3). The total score range lies between 0 and 63, and higher scores are consistent with more severe depression. The BDI-FS<sup>181</sup> has 7 components, and the total

score ranges from 0 to 21. In the dialysis patient population, the tool was validated against BDI with a threshold of 16 and 4 in the BDI and BDI-FS, respectively.<sup>187</sup>

It has been recommended by the KDOQI guidelines that dialysis patients be screened for depression and anxiety at dialysis initiation and every six months hereafter.<sup>64</sup> Earlier stages of CKD might also require an evaluation for depression as a part of standard care; however, routine screening for depression in those with stages 1 through 4 CKD patients has not been recommended by the KDOQI guidelines.<sup>188</sup> Nevertheless, the effectiveness of regular screening for depression has not been well proven, since there are no studies indicating better patient-oriented outcomes associated with regular screening.

### **2.2.3 Methods for Measuring Quality of Life**

Quality of life may be measured by questionnaires, and there is no gold standard for the measurement. The Short Form 36 Quality of Life Health Survey Questions (SF-36),<sup>15</sup> Kidney Disease Quality of Life Short Form (KDOQL-SF), and Euro-QoL-5 Dimension (EQ5D) are commonly used questionnaires. The EQ5D has five components, which cover mobility, self-care, usual activities, pain, and depression.<sup>189</sup> The tool is not commonly used in CKD patients. SF-36 has generic and disease specific forms, and has been validated for dialysis patients.<sup>190</sup> The disease specific form is called the Kidney Disease Quality of Life Short Form (KDOQL-SF).<sup>191</sup> It encompasses the general scale version 1.0, and the disease specific scale items based largely on symptoms that might be experienced by CKD patients. The drawbacks of the version 1.0, described in the following pages, might apply to the KDOQL-SF. Moreover, the time required to

complete the KDOQL-SF questionnaire makes implementation cumbersome and impractical.

We used the SF-36 version 2.0 in this study, and the tool has been validated for CKD patients, which only included the dialysis patient population.<sup>180</sup> Physical functioning was assessed by an accelerometer in the validation of the SF-36.<sup>190,192</sup> We decided to use the tool in our study because of ease of use, widespread use in chronic disease populations, and availability of norm-based comparisons.

The SF-36 (Medical Outcomes Trust, Boston, MA) contains 36 questions and can be used for comparing populations, screening patients, and comparing the health benefits of different treatment options.<sup>15</sup> The tool exists in a developmental form (1988), a standard form version 1.0 (1990), and a standard form version 2.0 (1998).<sup>193</sup> Both standard forms have versions based on four-week recall and based on one-week recall.<sup>194</sup>

The SF-36 version 2.0, also called the international version, was developed to increase reliability and validity of the instrument. It has the same number of questions as version 1 and is considered superior due to the improvement in the layout and delivery of the questionnaire, which includes instructions, item wording, and response categories. The questions and responses are formatted horizontally in version 2.0 while the previous version had a mixture of horizontal and vertical formats, which reduces the clarity of the meaning, especially for elderly respondents.<sup>193</sup>

In addition to improvements in the layout of the previous version of the instrument, several modifications were also implemented in the delivery of the questionnaire.<sup>193,194</sup>

Larger type size and bolding of instructions are among these changes.<sup>193,194</sup> Moreover, several wording changes to clarify understanding were also made in version 2.0.<sup>193,194</sup> One of the examples of these changes in item wording took place in question three, which measures physical activity.<sup>193,194</sup> The term “one block” was replaced with one hundred yards, and the term “several blocks” was replaced with several hundred yards.<sup>193,194</sup>

In the later version, two changes occurred in the response categories: replacement of dichotomous response with five-level response in the role physical and role emotional scales and replacement of six-level response with five-level response in the mental health, and vitality scales.<sup>193</sup> Firstly, the response choice for the role functioning scale, which included role physical and role emotional, was initially a binary variable.<sup>193</sup> A five-level categorical rating scale was adopted for the frequency of role limitation in the newer version.<sup>193</sup> This change was associated with increased score precision and reliability.<sup>193</sup> Secondly, limitations in vitality and mental health were included in question nine, and the six- response choice was reduced to five to simplify the format.<sup>193</sup>

The SF-36 form has 36 questions, eight scales, and two summary measures. The eight scales are as follows: physical functioning (PF), role physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role emotional (RE), and mental health (MH). PF, RP, and BP contribute to the physical component summary (PCS), whereas MH, RE, and SF contribute to the mental component summary (MCS). VT, GH, and SF contribute to both summary measures.<sup>193,194</sup>

In both versions of the SF-36, it is possible to perform the original standard 0–100 scoring and norm-based scoring. The norm-based scoring employs a linear transformation of the scores from the original scoring system to generate a mean of 50 and SD of 10 in the general US population. Normative data for the SF-36 were also published for the Canadian population.<sup>195</sup> Thus, the same mean and SD are applied to all scales, which simplifies the interpretation of the scores and enables comparison of scales, summary measures, and the two versions.<sup>193</sup>

Since the average score and SD for the calculation of each scale is different, the interpretation may be difficult in the standard scoring system.<sup>194</sup> In norm-based scoring, on the other hand, a constant mean and SD are applied to all scales.<sup>194</sup> A score higher than 50 is deemed above the general population norm, while a score of less than 50 is considered below the general population norm.<sup>194</sup> Overall, the major effects of the disease, in terms of the impact on the components of quality of life, are reflected in the profile of scores across the scales.<sup>194</sup>

Further, the norm-based scoring enables comparison of the components and the two versions of the tool by reducing ceiling and floor effects.<sup>194</sup> The SF-36 encompasses questions with wide and narrow score ranges.<sup>194</sup> The former yields a high ceiling whereas the latter sets the ceiling low.<sup>194</sup> As a result, the scales introduce peaks and valleys, which reflect both the actual difference in disease effect and arbitrary differences between ceilings and floors due to the differences in the response range.<sup>194</sup> The norm-based scoring system eliminates the random difference in ceiling and floor values that is unrelated to health outcomes.<sup>194</sup> As a result, unbiased representation of peaks and valleys

enables comparison of scales, summary measures, and versions 1.0 and 2.0. This is not possible in the standard scoring system.<sup>194</sup> Because of these reported advantages, norm-based scores were employed in the analysis of this study.<sup>193</sup>

The scoring of the instrument employs several steps.<sup>194</sup> Each response choice is assigned a precoded value.<sup>194</sup> The processing of the questionnaire starts with the data entry of precoded values into the system followed by an evaluation for missing and out of range values.<sup>194</sup> Scale scoring is the next step for producing a final value for each scale. BP, HT, and some items of GH, VT, SF, RE, and MH are reverse-scored and recoded to compute a final item value for each component of the scales.<sup>194</sup> The rest of the items retain the original precoded value.<sup>194</sup> A sum of final values for each item within each of the scales gives the raw score for each scale.<sup>194</sup> Thus, all items in each scale are summed to obtain raw scale scores. Consequently, raw scale scores are transformed to a 0–100 scale called the transformed scale score.<sup>194</sup>

Finally, norm-based scale scores are produced by a second transformation to a mean of 50 and SD of 10 in the general US population after z-score standardization is applied to the scales. Computation of the physical and mental components is the last step for the scoring of the instrument. High scores indicate better physical functioning, general health, vitality, social functioning, role emotional functioning, and mental health, while higher pain scores indicate a lack of pain.<sup>193,194</sup>

**Step 1: Transformation:**<sup>194</sup> Transformation to a 0–100 scale:<sup>194</sup> Transformed scale=  
[(Actual raw score-lowest possible raw score)] / [Possible raw score range] \* 100.

**Step 2: Standardization:**<sup>194</sup> Formulas for z-score standardization of SF-36v2 scales employ means and SDs from the 1998 general US population. The difference between the raw scale score and the mean is divided by SD to obtain z-score standardization.<sup>194</sup>

**Step 3: Transformation:**<sup>194</sup> Norm-based transformation of each scale of SF-36v2 z-scores is computed as follows: z-score of each scale is multiplied by ten and then the total value is added to 50.<sup>194</sup>

**Step 4: Aggregation of scale scores to compute the physical and mental health components:**<sup>194</sup> A prespecified coefficient value is multiplied by each standardized scale score and the resulting products are then summed across all the scales that contribute to PCS and MCS scores, whichever is being computed.

**Step 5: T-score transformation of component scores:**<sup>194</sup> Aggregate physical and mental component scores are multiplied by ten and added to 50 to produce transformed component scores (PCS and MCS).<sup>194</sup>

The software for the scoring of the tool (QualityMetric Health Outcomes™ Scoring Software 4.5) was recently developed, and a comma-separated-values (CSV) format of the excel sheet can be uploaded into the instrument.<sup>196</sup> The scores, both standard and norm-based, are provided instantly. The software is designed to eliminate bias due to missing data. It is also convenient and reduces the chance of incorrect calculations.

## **2.3 The Rationale for the Study**

### **2.3.1 Existing Literature in the Area of Chronic Kidney Disease and Dialysis**

#### **2.3.1.1. Sleep Disturbances**

Sleep disorders are much more common in patients with CKD, and the prevalence rate was shown to be 44% in a systematic review.<sup>197</sup> This was consistent with other studies that reported 50% prevalence in dialysis patients.<sup>198-202</sup> Restless leg syndrome, sleep apnea, sleep disruption, metabolic changes due to kidney failure, medications, poor sleep hygiene, and depression were indicated as underlying reasons for this high frequency of sleep disorders.<sup>199-202</sup> It was shown that sleep quality improved after dialysis dose was increased in PD patients.<sup>203</sup> Overall, hypnotic use for sleep disturbances was reported 26% to be in CKD patients.<sup>204</sup>

There are conflicting reports regarding the association of sleep quality, quality of life, and survival in dialysis patients. Insomnia was associated with lower quality of life in addition to lower survival rates, according to several reports.<sup>199-202</sup> In contrast, poor sleep was not correlated with an increased risk of death, according to a study that included 128 HD patients.<sup>205</sup> Parker et al. studied 46 HD patients for sleep quality and quality of life. In accordance with the previous study, quality of life scores were not associated with polysomnography measurements.<sup>206,207</sup> As a result, there are several studies for, and few studies against, the hypothesis regarding the correlation between sleep quality, longevity and life quality in patients on dialysis.

Sleep architecture is also affected as a result of neurohormonal changes in CKD, according to several reports.<sup>198</sup> Jurado-Gamez et al. studied the architecture of sleep in 32 HD patients, and 19 healthy controls with a sleep study.<sup>198</sup> REM and sleep efficiency were shown to be lower,<sup>206,198</sup> while sleep latency and stage 1 NREM sleep were longer in the dialysis group.<sup>198</sup> Longer stage 1 and stage 2 NREM sleep, and lower sleep efficacy were also reported in dialysis patients.<sup>208</sup> The evidence suggests that sleep structure is affected in CKD patients.

Another area of interest for many researchers is correlates of poor sleep quality in dialysis patients. According to a study report, gender, marital status, hemoglobin, and albumin were not associated with poor sleep, while young age was.<sup>205</sup> In contrast, age and smoking have been associated with an increased risk for poor sleep quality.<sup>209</sup> Malnutrition and high calcium phosphate product have been linked to impaired sleep in PD patients.<sup>177</sup> Cengic et al. underscored the link between high phosphate and high PTH levels with sleeping problems in HD patients.<sup>210</sup> Depression was reported as one of the predictors for impaired sleep in a CKD study cohort.<sup>211</sup> Additionally, dialysis shift in the morning was also correlated with impaired sleep, according to the report from a large study cohort.<sup>209</sup> Dialysate temperature was also tested as a modifier for poor sleep quality. It was suggested that HD with cool dialysate could improve sleep by decreasing sympathetic activity.<sup>212</sup>

Sleep apnea is a condition that contributes to poor sleep, and is common among CKD patients. Sleep apnea was indicated as one of the most prevalent sleep disorders among that population.<sup>197</sup> Kimmel et al. studied 26 hemodialysis patients and performed

polysomnography that indicated 73% of patients had sleep apnea.<sup>213</sup> These findings were similar to other studies that included HD patients, and supported higher prevalence rates.<sup>198,214</sup> Additionally, HD patients have an approximately four-fold increased risk for severe sleep apnea, when compared to the age, gender, and BMI matched control group.<sup>215</sup>

Correlates of sleep apnea have been studied in CKD patients. Obesity has been associated with a high risk for sleep apnea in dialysis patients.<sup>216,217</sup> Central obesity was also suggested as a predisposing factor in kidney patients.<sup>218</sup> According to a recent report, PD patients indicated a higher prevalence of sleep apnea than HD patients.<sup>219</sup> In contrast, dialysis modality was not associated with the prevalence and severity of sleep apnea in dialysis patients.<sup>220</sup> Clinical consequences of sleep apnea include increased risk for cardiovascular complications,<sup>108,109</sup> systematic and pulmonary hypertension<sup>106,110,111</sup>, and lower survival rates.<sup>112</sup>

Different from the general population, central and mixed sleep apneas are more common in kidney patients. Of 11 dialysis patients, 7 had mixed (central and obstructive) sleep apnea, according to a report from Miskowiec et al.<sup>78</sup> Other reports also supported the high prevalence of central sleep apnea among HD patients.<sup>198,208</sup> The uremic toxins are held responsible for the high proportion of central sleep-disturbed breathing disorder in CKD patients.<sup>198,208</sup>

In addition to higher prevalence rates and our lack of knowledge about predictors of sleep apnea in kidney patients, the disease can be under-diagnosed as patients can fail to exhibit

the usual symptoms of the disease.<sup>43</sup> Beecroft et al. studied 76 dialysis patients to examine the difference in clinical presentations between the groups in a case-control design (n: 380).<sup>43</sup> A sleep study and Epworth Sleepiness Scale were employed in the study.<sup>43</sup> Snoring, witnessed apnea during sleep, and daytime sleepiness were less frequent in dialysis patients.<sup>43</sup> This study indicated that sleep apnea might be under-diagnosed due to atypical presentation. Additionally, it was shown that dialysis patients with sleep apnea had a lower BMI than the control group, which consisted of sleep apnea patients with normal kidney functions.<sup>43</sup>

Overall, CKD patients are prone to sleep disturbances that result in poor sleep quality.<sup>197</sup> Inadequate sleep is the root of the problem that ranges from accidents to long-term health effects including hypertension, as well as lower quality of life and life expectancy.<sup>92,112,107</sup> Sleep apnea is one of the most common causes for sleep disorders, and can be left unrecognized due to atypical presentation in kidney patients.<sup>43</sup> Although the determinants of the disease are well-defined in the general population, a lack of evidence supporting the correlates in CKD patients necessitates further investigations in that area. Furthermore, most of the data are from the dialysis population, and identifiers of poor sleep quality in non-dialysis CKD patients also requires more research.

#### **2.3.1.2. Depression**

The prevalence of depression is reportedly higher in patients with kidney failure, and has been studied previously. Balogun et al. studied approximately 600,000 non-dialysis CKD patients with a five-year follow-up period.<sup>221</sup> The overall prevalence of depression was

indicated as 30%, which was considerably higher than the normal population.<sup>221</sup> The diagnosis of depression was based on the structured clinical interview and/or reported antidepressant medication use.<sup>221</sup> Su et al. studied 320 HD patients and employed BDI for depression screening.<sup>18</sup> The prevalence of depression was 23.9% in those who received conventional HD.<sup>18</sup> Cilan et al. studied 40 PD patients, and found that 25% of patients were depressive, when BDI was employed as a screening tool.<sup>19</sup> These results were in line with other studies related to depression in dialysis patients.<sup>20</sup> Saeed et al. screened 180 HD patients for depressive disorder using BDI with a high prevalence rate (75%).<sup>222</sup> Similarly, the prevalence of depression was 61.4% in HD patients with a 16 cut-off in BDI.<sup>223</sup> BDI provided only 4% false-positive cases in a group of HD patients, and the actual rate of depression was 26%.<sup>224</sup>

In addition to the higher prevalence rates, the health outcomes of depression in kidney patients were also studied. Peritonitis rates were higher in those with depression in a study cohort.<sup>225</sup> This was confirmed by a previous report.<sup>226</sup> Depression might also affect quality and longevity of life in CKD patients.<sup>180</sup> Feng et al. studied 362 adult CKD patients. The prevalence of depression was 13%, and correlated with a lower quality of life.<sup>227</sup> However, those with depression did not indicate lower survival rates in a four year follow-up period (OR: 2.62, 95% CI: 0.77–8.89, P: 0.13) after adjusted analysis.<sup>227</sup>

Contrary to these findings, Tsai et al. included 428 non-dialysis CKD patients to examine the association of depression with survival. A total of 37% of patients had depressive symptoms with the BDI. In unadjusted models, the hazard ratio for death was 2.63 (95% CI: 0.99–6.91) in depressive patients.<sup>228</sup> Depression could be associated with the

comorbidities that lead to death, since diabetes, history of depression, and other psychiatric illness were significantly higher in the depression group as compared to the non-depressive group. These findings were in line with other studies that examined the relationship between depression and mortality.<sup>221,229</sup> After adjustments were made for comorbidities, mortality was significantly higher in those with depression, according to a recent report that included a large CKD study cohort.<sup>221</sup> It was also reported in the same report that age-adjusted survival rates were significantly lower in those with depression (hazard ratio: 1.55, 95% CI: 1.54–1.57,  $P < 0.001$ ).<sup>221</sup>

Correlates of depression such as age, comorbid conditions, seasonality, eGFR, and renal disease progression were also examined in few studies in CKD patients. An association between young age and comorbid conditions with depression was indicated.<sup>221</sup> Patients with depression indicated a higher incidence of diabetes and coronary artery disease when compared to those without depression in a study cohort that included 162 PD patients.<sup>225</sup>

The seasonality of depression was also studied in patients with kidney failure.<sup>230</sup> A total of 66 kidney failure patients were included, and BDI was performed in June and January to test seasonal fluctuations in mood.<sup>230</sup> PCS and BDI scores were significantly lower in June.<sup>230</sup> Depression and eGFR were not correlated, according to the findings from Feng et al., whereas eGFR was linked to an increased risk for depression in a large study cohort.<sup>227,231</sup> Depression was indicated as an independent risk for renal disease progression and death in a report by Tsai and others.<sup>228</sup>

There are controversies around the safety and efficacy of the antidepressant medications in CKD patients.<sup>232</sup> Nagler et al. performed a systematic review that included a total of 28 studies to test the efficacy and safety of antidepressant treatment in stage 3-5 CKD patients.<sup>232</sup> Except for three studies, sample size was lower than 20.<sup>232</sup> It was indicated that the elimination half-life was increased while clearance was decreased for some of the antidepressant medications.<sup>232</sup> It was also suggested that pharmacokinetic changes might be significantly different in kidney patients, and treatment did not show any significant clinical effect with antidepressant, when compared to a placebo.<sup>232</sup> The lag time for clinical improvement was 3-6 weeks in the general population while in CKD it could be up to 12 weeks.<sup>232</sup>

Due to different pharmacokinetics and increased lag time for clinical improvement, antidepressants should be administered with extreme caution in CKD patients.<sup>232</sup> The Chronic Kidney Disease Antidepressant Sertraline Trial is a randomized double blinded placebo controlled trial for safety of Sertraline treatment in stage 3-5 CKD patients with depression.<sup>233</sup> The study has not been completed yet, but it is expected to add valuable information in regards to management of depression in kidney patients.

### **2.3.1.3. Quality of Life**

Quality of life has been reportedly low in patients with CKD<sup>234</sup>, and various determinants of quality of life in CKD patients have been previously studied including anemia, stages of CKD, and dialysis modalities.<sup>235-238</sup> Firstly, early and complete correction of anemia has been associated with better life quality indexes.<sup>235,239</sup> The Cardiovascular Risk

Reduction by Early Anaemia Treatment with Epoetin Beta study indicated early treatment of anemia was correlated with a significant effect.<sup>235</sup> A multicentre study included 596 hemodialysis patients, who had no symptomatic cardiac disease, in a randomized controlled trial. Complete correction of anaemia was associated with higher energy scores.<sup>239</sup>

Further, the stage of CKD has been associated with quality of life scales. SF-36 was employed in a cohort of 634 CKD patients.<sup>236</sup> Based on the historical data, comparison was made between the CKD group, HD patients, and healthy control.<sup>236</sup> CKD patients exhibited significantly higher scores when compared to the HD population ( $P < 0.0001$ ) in this prospective observational study.<sup>236</sup>

Lastly, the difference in the quality of life between HD and PD treatments was also tested. Turkmen et al. studied 154 dialysis patients (64 PD and 90 HD patients) for quality of life, and indicated that PCS and MCS scores were significantly higher in HD patients.<sup>240</sup> Another multicenter study also supported the superiority of HD treatment in terms of PCS scores.<sup>237</sup> This was not in line with another study by Harris et al. that indicated no significant difference between dialysis modalities in quality of life.<sup>241</sup> Age and comorbid conditions might be major confounders that could affect quality of life.

Sleep quality and depression have been also correlated with a low quality of life in several studies.<sup>238,242</sup> Lee et al. studied 208 CKD patients, and indicated that depression was associated with lower quality of life scores.<sup>238</sup> Poor sleep quality was also related to a lower quality of life in dialysis patients.<sup>242</sup> This was supported by another report.<sup>243</sup> Poor

sleep quality, mental health, and quality of life were shown to be interrelated conditions in kidney patients.<sup>200</sup>

### **2.3.2 Gaps in Existing Literature**

Since sleep apnea is common, under-diagnosed, and related to life-threatening complications, the factors related to the disease have been areas of interest for many researchers.<sup>112,213</sup> Age, gender, and BMI are established risk factors for sleep apnea in the general population.<sup>29</sup> However, determinants of sleep apnea in CKD patients have not been well studied. Several studies indicated that the traditional factors were not well correlated with sleep apnea in kidney patients.<sup>213,244-247</sup> As a result, predictors of sleep apnea syndrome need to be explored in more detail in kidney patients.

Depression has been associated with higher morbidity and mortality rates in dialysis patients.<sup>248,249</sup> The condition has also been associated with low medication adherence in the dialysis population.<sup>250</sup> Physician-diagnosed depression and questionnaire based diagnose were compared in a large multicentre dialysis patient cohort, and it was shown that depression was under-diagnosed.<sup>251</sup> The link between early diagnosis and treatment of depression, and patient-oriented outcomes is yet to be discovered.<sup>248</sup>

Assessment and management of modifiable risk factors for sleep disturbances, depression, and quality of life is important in improving health outcomes and patient satisfaction.<sup>112,213,248,249</sup> Risk factors for these conditions are not well-known in CKD patients.<sup>244-247</sup> Further research is needed to establish algorithms for diagnosis and management of these comorbid conditions. Although use of the screening tools, such as

the BDI and SF-36, is recommended in the dialysis population, the implication of this practice for patient outcome is not clear.

### **2.3.3 Objectives of the Study**

The main objective of this study was to identify factors associated with sleep quality, sleep apnea, depression, and quality of life in kidney patients. The point prevalence of sleeping problems, including sleep apnea and depression, was studied. The correlation between sleeping problems, depression, and quality of life was also examined. The association between quality of life with eGFR and Hb was tested. Objectives of the study also included a comparison of correlates of poor sleep quality in the dialysis and non-dialysis groups. A summary of primary and secondary objectives follows:

#### **2.3.3.1 The Primary Objective**

1. To determine factors associated with sleep disturbances, depression, and quality of life among patients with chronic kidney disease.

#### **2.3.3.2 Secondary Objectives**

1. To assess the prevalence of sleeping problems, sleep apnea, and depression in CKD patients.
2. To test the correlation between sleeping problems, depression, and quality of life.
3. To test the association between e-GFR with sleeping problems and depression.
4. To test the association between hemoglobin with MCS and PCS scores.
5. To test the correlation between e-GFR with MCS and PCS scores.

6. To examine correlates of poor sleep quality in the dialysis and non-dialysis groups.

#### **2.3.4 The Hypothesis**

The cardiovascular disease risk has been reportedly high in patients with CKD<sup>188</sup>, and traditional and non-traditional cardiovascular disease risk factors need to be addressed in the management of these patients.<sup>188</sup> Psychosocial stress and physical inactivity are among traditional cardiovascular risk factors.<sup>188</sup> Since modifiable risk factors have been linked to negative health outcomes,<sup>252</sup> it was recommended that traditional cardiovascular disease risk factors be assessed in all CKD patients.<sup>188</sup> Assessment and modification of psychosocial factors and physical well-being twice a year, including depression, anxiety, and quality of life is recommended in dialysis patients.<sup>64</sup>

Since sympathovagal imbalance influences clinical phenomena such as hypertension, diabetes mellitus, CKD, depression, and sleeping problems, there should be correlations between these conditions. We hypothesized that sleeping problems and depression correlate with the degree of kidney dysfunction and hypertension, and these conditions might affect quality of life in CKD patients. As a result, sleep quality, depression, and quality of life should be inter-related in those with CKD. The prevalence of each of these conditions should be higher when kidney disease is more advanced, such as in dialysis stage. Estimated glomerular filtration rate was used for CKD definition and should be correlated with sleep quality and depression. To test the factors associated with sleep

quality, sleep apnea, depression, and quality of life, we conducted a cross-sectional study.

The hypothesis was summarized in the following page.

1. We hypothesize that the prevalence of impaired sleep will be higher in the group on dialysis than in those with less severe CKD.
2. We hypothesize that the prevalence of sleep apnea will be higher in the group on dialysis than in those with less severe CKD.
3. We hypothesize that the prevalence of depression will be higher in the group on dialysis than in those with less severe CKD.
4. We hypothesize that sleep quality will be correlated with eGFR, blood pressure, and presence of diabetes.
5. We hypothesize that poor sleep quality will be associated with poorer quality of life.
6. We hypothesize that sleep apnea will be associated with poorer quality of life.
7. We hypothesize that depression will be associated with poorer quality of life.

### **Chapter 3: METHODOLOGY**

This is a cross-sectional study of adult patients with stage 1 through 5 CKD recruited between September 2012 and December 2012. HD patients were recruited from the Health Sciences Centre, St. Clare's Mercy, and Waterford Hospitals' HD centres in St. John's, Newfoundland and Labrador, Canada. Patients with CKD, with or without a transplant, were enrolled in the Waterford Hospital outpatient nephrology clinics. PD and home HD patients were also recruited from the Waterford Hospital outpatient clinics.

Kidney dysfunction was defined by an e-GFR calculated with the MDRD formula. Inclusion criteria included (i) being an adult patient (18 years or older), (ii) having some degree of kidney dysfunction with an eGFR cut-off of 60 ml/min/1.73m<sup>2</sup>, and (iii) living in the St. John's area. Exclusion criteria included (i) severe vision and/or hearing problems that interfere with the informed consent process and (ii) choosing to decline research participation.

This study was approved by the provincial Health Research Ethics Authority and Research Proposal Approval Committee of Eastern Health. Each patient was approached by a member of the care team to obtain initial consent before being approached by the researcher. The informed consent process was completed after sufficient information was given and written consent obtained by the primary investigator. The questionnaires were administered by the principal investigator, who read out the statements and asked the participants to choose the most appropriate response for his or her current condition. Consequently, the selected statement was circled. The questionnaires were self-

administered by those who did not require any assistance. The duration of interviews ranged from 20 to 45 minutes.

The instruments that were employed in this study were the PSQI,<sup>14</sup> BQ,<sup>17</sup> BDI,<sup>184</sup> BDI-FS,<sup>187</sup> and SF-36.<sup>15,190</sup> Each questionnaire was scored for each participant. BDI-FS instrument was scored by the principal investigator after the interview was completed. The attending nephrologist was notified if a patient's results showed a significant depression risk and/or high risk for sleep apnea. A decision for a psychiatry consultation and/or sleep study order was at the discretion of the attending nephrologist.

A case report form (Appendix A) was developed for this study, on which we recorded patient's age, sex, race, marital status, weight, height, presence of diabetes mellitus, current CNS medication use, dialysis vintage, and details of the dialysis prescription, including recent predialysis weight and average interdialytic weight gain in the week prior to the study measurements. Several laboratory parameters were also recorded, and a detailed explanation is provided in the following pages. The patient's sitting blood pressure prior to the interview was also recorded. Each participant was given a unique identification number to protect confidentiality. The inventory of participants and associated identification numbers were kept in a secure place. Electronic files were kept under password protection.

### **3.1 Data Collection**

Baseline data collection following informed consent included administration of questionnaires, blood pressure measurements, and anthropometric measurements (weight,

height). Chart review was also performed for the parameters as described in the following pages. Demographic variables including age, gender, and marital status were registered for each participant. After data entry was completed, 15% of cases were randomly selected, and all variables related to these cases were rechecked. The rate for incorrect entry was 1%.

## **3.2 Definitions of Exposures and Covariates**

### **3.2.1 Race**

Participants were divided into two groups—Caucasian or non-Caucasian—under the race category. Since only two participants were non-Caucasian, race was not tested as a predictor.

### **3.2.2 Marital Status**

According to the information about marital status, participants were categorized into two groups. Those who were married or had a common-law partner were included in one group. Participants who were single, widowed, or divorced were included in the other group. The reason for this assignment was to test the significance of relationship status on sleep quality.

### **3.2.3 Chronic Kidney Disease**

CKD was defined by an eGFR estimated by an MDRD<sup>32</sup> approach. Kidney dysfunction was categorized with eGFR, according to the severity of damage as follows: stages 1 and 2 (eGFR  $\geq$  60ml/min/1.73m<sup>2</sup>), stage 3 (eGFR 30—59 ml/min/1.73m<sup>2</sup>), stage 4 (eGFR

15—29 ml/min/1.73m<sup>2</sup>), and stage 5 eGFR (< 15ml/min/1.73m<sup>2</sup>). Those with eGFR ≥ 60ml/min/1.73m<sup>2</sup> had either abnormal urine or kidney imaging tests. Patients were also further classified as dialysis and non-dialysis groups. Dialysis treatments included in-center and home-based dialysis treatments: home-HD and peritoneal dialysis.

### **3.2.4 Diabetes Mellitus**

Diabetes mellitus was defined as a binary variable (yes/no). Self-reported cases and those who were on either insulin or one of the oral anti-hyperglycemic agents were considered diabetic. Cases with type 1 and type 2 diabetes were included under one category. Detailed reports identifying all co-morbidities were not available, especially in non-dialysis patients. As a result, only diabetes mellitus and hypertension were included as co-morbid conditions.

### **3.2.5 Obesity**

A BMI was calculated with the following formula: weight (Kg) / height<sup>2</sup> (m<sup>2</sup>). Obesity was defined using BMI, with values more than 30 Kg / m<sup>2</sup> considered obese.

### **3.2.6 Smoking Status**

Patients were asked about their smoking status. Those who never smoked and those who smoked in the past, but quit were grouped in one category. Current smokers were grouped in the other category.

### **3.2.7 Blood Pressure Control**

Blood pressure recordings of more than 135/85 mmHg or less than 110/60 mmHg were considered abnormal. The sitting predialysis blood pressure was recorded for dialysis patients. Sitting blood pressure measurements before the doctor's visit were also recorded for ambulatory care patients. Blood pressure was measured with an automated machine by a registered nurse or licensed practical nurse after a five-minute rest. If the reading for systolic blood pressure was  $\geq 135$  mmHg or diastolic blood pressure was  $\geq 85$  mmHg, blood pressure was considered high and poorly controlled. Furthermore, those with systolic blood pressure with less than 110 mmHg and/or diastolic blood pressure less than 60 mmHg were also included in the low and poorly controlled blood pressure category. Those with values less than 135 mmHg and higher than 110 mmHg for systolic blood pressure, and less than 85 mmHg and higher than 60 mmHg for diastolic blood pressure were included in the well-controlled blood pressure category.

### **3.2.8 The Mean Arterial Pressure**

The mean arterial pressure was calculated for each participant with the following formula:

$$[(2 * \text{diastolic blood pressure}) + \text{systolic blood pressure}] \div 3$$

Sitting systolic and diastolic blood pressures on the day of the interview were used in the calculation.

### **3.2.9 The Pulse Pressure**

The pulse pressure was calculated with the following formula:

[Systolic blood pressure – diastolic blood pressure]

Sitting systolic and diastolic blood pressures on the day of the interview were used in the calculation.

### **3.2.10 Central Nervous System Medication Users**

CNS medications included benzodiazepine hypnotics, non-benzodiazepine hypnotics, and antidepressants. Antipsychotics, anticonvulsant agents, and opiates were not registered. Only seven patients were on an antipsychotic treatment (five CKD and two PD patients), and not included under the CNS medication category. Opiate use was not included due to missing data. Data were not available to classify alcohol use either. Prescription data was taken from the medical charts, not by patient history. Medical data related to opiate and alcohol use were incomplete, especially for the non-dialysis group.

### **3.2.11 Laboratory Data**

Laboratory data included parathyroid hormone (PTH), calcium (Ca), phosphate (P), albumin, glucose, hematocrit (Hct), hemoglobin (Hb), and e-GFR for non-dialysis group. Excluding PTH, the value closest in time to the interview within the window plus or minus three months was collected. Values within six months of the interview day were recorded for PTH. However, all values excluding PTH were within a one-month period for dialysis and transplanted patients. Serum calcium level was corrected with the

following formula: serum calcium (mmol/L) + 0.02 \* [40-patient's serum albumin (g/L)]. PTH, Ca, P, and Hb have been associated with sleep quality in CKD patients as indicated in the literature review.

### **3.2.12 Dialysis Status**

Dialysis status was also recorded in the following manner: dialysis positive group included those who were on HD or PD.

### **3.2.13 Dialysis Vintage**

This variable was only applied to dialysis patients by recording the time, in days, since the first dialysis treatment started.

### **3.2.14 The Vascular Access**

This variable was only applied to HD patients. The access type included arteriovenous (AV) fistula, arteriovenous graft, and catheter including temporary and permanent. The type of the vascular access was categorized as catheter and AV fistula in this study cohort, as none of our patients had an AV graft. Catheter access might be a marker for poorer overall health.

### **3.2.15 Peritoneal Dialysis Modalities**

This variable was only applied to PD patients. Continuous ambulatory peritoneal dialysis (CAPD) and automated peritoneal dialysis were two modalities (APD) for PD patients.

### **3.2.16 The Interdialytic Weight Gain**

This variable was only applied to HD patients. The interdialytic weight gain (IWG) equals to sum of the net ultrafiltration per dialysis session in the last six dialysis sessions including the day of the interview divided by 6.

### **3.2.17 The Sleep Quality**

A global score was obtained for each participant by adding the scores from seven components of the PSQI. Scores higher than 5 were considered to indicate poor sleep, while scores equal to or lower than 5 were considered good sleep. When the global score was examined as a continuous variable, higher scores indicated worse sleep quality, whereas lower scores suggested better sleep quality.

### **3.2.18 Sleep Apnea**

The Berlin Questionnaire was used to assess the risk status for sleep apnea.<sup>17</sup> The instrument indicated high or low risk for sleep apnea, and each category was assigned a dummy variable.

### **3.2.19 The Beck Depression Inventory**

A cut-off value of 16 was employed in the current study for the BDI, and a global score of 4 or more was considered as positive for BDI-FS.<sup>181,187</sup> The questionnaire was scored on the day of the administration. The attending nephrologist was notified about those with

positive test results for depression. A psychiatric referral was at the discretion of the physician.

### **3.2.20 Quality of Life**

A license from QualityMetric was obtained for the administration of the SF-36 forms.<sup>15</sup> The QualityMetric Health Outcomes™ Scoring Software 4.5 was also provided by QualityMetric. A four-week recall form of the SF-36 version 2 was employed in this study. Scores were calculated using norms for Canada. An Excel database (Microsoft Corp, Seattle, WA, 2010) was used for initial data entry and data preparation for analysis. A conversion was made to a comma-separated value (CSV) format before the data was uploaded into the software. Original 0–100 scoring and norm-based scoring were performed with the Scoring Software 4.5. Subsequently, the relevant data were uploaded into an SPSS data file (SPSS, version 20.0, Chicago, IL). Eight health domains and two summary measures were calculated. The norm-based scores were included in the analysis due to the advantages that were mentioned previously.

### **3.3 The Research Question Overview: Population, Comparison, Exposure, Outcome, and Time (PICOT)**

The PICOT approach was adopted for the development of the research question. The population consisted of adult CKD patients. Primary exposure was kidney dysfunction. Covariates included age, gender, BMI, diabetes mellitus, smoking, SDP, DBP, MAP, PP, blood pressure control, CNS medication use, Hb, and receiving dialysis treatment. Sleep quality, sleep apnea, depression, and quality of life were the main outcomes. The PSQI,<sup>14</sup>

BQ,<sup>17</sup> BDI,<sup>184</sup> BDI-FS,<sup>181</sup> and SF-36 questionnaires<sup>15</sup> were employed as measurement tools in this study. Since this was a cross-sectional study, exposures and outcomes were measured simultaneously.

### **3.4 The Analytical Plan**

The analytical plan included descriptive and inferential statistics. Firstly, descriptive statistics for central tendency (mean, median, and mode), dispersion (minimum, maximum, and standard deviation), and distribution (skewness and kurtosis) were the initial steps for analysis. Consequently, mean values (standard deviation; SD) for normally distributed and median values (inter-quartile range; IQR) for non-normally distributed continuous variables were used to summarize the values. Frequencies (numbers) and proportions were used for categorical variables in the dialysis and non-dialysis groups.

Secondly, if the assumption of equal variances between the two groups was met, the initial step for the inferential statistics was the comparison of means for continuous variables with a student t-test; otherwise, a nonparametric test was employed for the comparison (Mann-Whitney U test). The Levene's test was used to test the equal variance assumption with a significance level of 0.05. Frequency distributions for categorical variables were compared with the Pearson chi-square test between the groups. If the chi-square test assumption was violated (all expected cells had to be more than 5, as degrees of freedom was 1 for a 2 x 2 table), Yates' correction was planned to be a substitute for the Pearson test.

Thirdly, associations between poor sleep quality, risk of sleep apnea, and depression in the study cohort were sought with demographic characteristics and laboratory data. Age, gender, marital status, BMI, presence of diabetes mellitus, current smoking status, level of blood pressure control, MAP, PP, Hb, eGFR, stage of CKD, BQ, BDI, BDI-FS, PCS, and MCS have been tested for an association with sleep quality. Further, associations of PCS and MCS scores with sleep quality, risk for sleep apnea, depression, and all covariates were tested using Spearman's correlation coefficient tests.

Furthermore, the hypothesis of "sleep quality" can be predicted by age, gender, BMI, presence of diabetes, current smoking status, level of blood pressure control, MAP, PP, SBP, DBP, CNS medication use, dialysis treatment status, stage of CKD, eGFR, Hb, BDI, BQ, PCS, and MCS" was tested in this study cohort. Since there was only one outcome variable, simple linear or nonlinear regression could have been employed. The outcome variable was dichotomous; as a result, logistic regression models were employed that accommodated multiple predictors. Since a non-linear model was employed, confidence intervals that included 1 were considered as non-significant. Model significance was tested by the Omnibus test, Hosmer-Lemeshow test and -2loglinear likelihood ratios (-2LLR). Cox-Snell  $R^2$  and Nagelkerke  $R^2$  were considered as the equivalent to  $R^2$  in the linear regression. Significance of individual coefficients was tested by the Wald statistic technique, and odds ratios with 95% confidence intervals (CI) were obtained.

Assumptions were tested, and residual analysis was performed to evaluate the model. Since the linearity assumption was violated for MCS scores, quartiles ranges were used to

categorise the variable. Category 1 (percentile < 25%) included values less than 49.4, category 2 (percentile 25%–50%) included values between 49.4 and 55.5, category 3 (percentile 50%–75%) included values between 55.5 and 59.5, and category 4 (percentile > 75%) included 59.5 and 73. Subsequently, MCS score was used as a categorical variable in the multivariate and reduced models. A difference contrast (reverse Helmert contrast) method was selected to compare the categories of MCS with the mean of the previous categories of the variable in the logistic regression technique.

Two-sided tests were employed with a significance level of 0.05. Imputation for missing data was not performed. The percentage of missing data was between 0% (age, gender, dialysis status, the PSQI, and the BQ questionnaires) and 11% (phosphate) in the study cohort. Finally, subgroup analysis was performed for the dialysis and non-dialysis groups. Characteristics of the cohorts were examined. Further, comparisons between the groups with poor and good sleep quality were made.

### **3.5 Statistical Analyses**

All data analyses were performed using IBM SPSS Statistics 20, Release Version 20.0 (SPSS, Inc., 2011, Chicago, IL, [www.spss.com](http://www.spss.com)).

### **3.6 Preparing the Data**

The information was compiled in Excel spread-sheets initially. Before the raw data was transferred to SPSS, the data set was cleaned, recoded, and prepared for analysis. The correlation analysis included the presence of depression, high risk for sleep apnea, poor

sleep quality, and PCS and MCS scores as outcome variables. One outcome variable and 19 explanatory variables were employed in the univariate logistic model (table 3.9). The dependent variable was the nominal binary variable (dichotomous), while 50% of the independent variables were categorical.

In the Logistic Models, the outcome variable was expressed as good or poor sleep quality with a threshold of 5 for the global PSQI score. As a result, a censoring dichotomy was used to produce two-level variables by a critical value for the outcome variable. A censoring dichotomy was also applied to BDI and BP control. The rest of the categorical response variables had a natural dichotomy, and all were coded as dummy numbers “0” or “1”. No modification took place for two continuous variables; nevertheless, the distribution and outliers were determined by using a histogram. The SF-36, BDI, and BDI-FS questionnaires were scored and registered as quantitative continuous variables in the dataset. The detailed explanation of the coding process was provided in the data view of SPSS.

The first step was to test the model fit reliability to indicate if at least one of the predictors was related to the outcome. Afterwards, hypothesis testing was performed. Lastly, the assumptions for the logistic regression were tested to assure the results were valid and generalizable to other populations. The details are given in the results section.

## **Chapter 4: RESULTS**

### **4.1 Descriptive Statistics**

Demographics and patient population: A total of 303 patients (125 females, 178 males with mean age  $62.7 \pm 14.5$  years) were included in this cross-sectional study (please see table 4.1). The overall participation rate, which was defined as the total number of patients who did not refuse consent divided by the total number of patients who were approached by a team member on that particular day, was 35.2% in ambulatory care patients and 50% in hemodialysis patients. The total of 202 patients (86 females, 116 males, mean age  $63.8 \pm 14.4$ ) had non-dialysis CKD, and 18 patients had a kidney transplant. A total of 101 patients (39 females, 62 males, mean age  $60.6 \pm 14.4$ ) were on dialysis; 7 patients were on PD, 2 patients were on home HD and 92 patients were in-centre HD treatments. The vast majority of the participants (n: 301; 99%) were categorized as Caucasian, while only two people were non-Caucasian. A total of 186 (61.4%) participants (65; 64.4% in the dialysis group and 121; 59.9% in the non-dialysis group) were married or had a common-law partner.

Participants were also divided into five groups according to eGFR. Stage 1 and 2 needed to be collapsed into one category as eGFR was only reported as more than  $60\text{ml}/\text{min}/1.73\text{m}^2$ , and it was not possible to further specify the results as stage 1 or 2. A total of 39 patients were in stage 1 and 2: 79 in stage 3, 68 in stage 4, and 112 in stage 5. Five people were missing a valid eGFR.

CNS medication users were also registered. A total of 94 (31%) patients were on hypnotics and/or antidepressant treatments. In the dialysis group 53 (52.47%) and in the non-dialysis group 41 (20.2%) participants were on a CNS medication. The Pearson Chi-square test indicated a significant difference between these groups (P: 0.0001). The dialysis group had a higher frequency in terms of a CNS medication use.

Of 303 participants, 293 patients had a blood pressure measurement and 76 (25.1%) patients were in the well-controlled category. A total of 166 (55%) patients had hypertension, and 51 (17%) patients had hypotension in the study cohort. In the dialysis group, 20 patients had normal blood pressure, while the number of patients with normal blood pressure was 56 in the non-dialysis group. The dialysis and non-dialysis groups were not significantly different (P: 0.13) in terms of the proportion of patients with well-controlled blood pressure.

An arteriovenous fistula was the method of choice for a vascular access in most of the HD patients. A total of 55 (58%) HD patients had an AV fistula, while 39 (42%) patients had a catheter. Of seven PD patients, three patients were on APD treatment, while four patients were on CAPD. Please see comparisons between the dialysis and non-dialysis groups in the table 4.1 for patient characteristics, and table 4.2 for laboratory data.

**Table 4.1 Baseline characteristics of the participants divided by dialysis status**

<b>Variable</b>	<b>Entire cohort (mean ± SD)</b>	<b>The dialysis group (mean ± SD)</b>	<b>The non- dialysis group (mean ± SD)</b>	<b>P<sup>a</sup></b>
<b>N</b>	303	101	202	
<b>Age (years)</b>	62.7 ± 14.5	60.6 ± 14.4	63.8 ± 14.4	0.07
<b>BMI (kg/m<sup>2</sup>)</b>	29.8 ± 6.5	29.4 ± 5.9	30 ± 6.7	0.43
<b>MAP (mmHg)</b>	91.4 ± 13.4	94.5 ± 16.8	89.7 ± 11	0.022 <sup>c</sup>
<b>PP (mmHg)</b>	72.4 ± 21.6	76.2 ± 23.2	70.5 ± 20.4	0.03
<b>Variable</b>	<b>Entire cohort N (%)</b>	<b>The dialysis group N (%)</b>	<b>The non- dialysis group N (%)</b>	<b>P<sup>a</sup></b>
<b>Female gender; n (%)</b>	125 (41.2%)	86 (43%)	39 (39%)	0.50
<b>Married or had a common law partner; n (%)</b>	186 (68%)	65 (64%)	121 (69%)	0.7
<b>Caucasian; n (%)</b>	301 (99.3%)	100	201	1 <sup>b</sup>
<b>Diabetes; n (%)</b>	141 (46.7%)	53 (52.5%)	88 (43.8%)	0.15
<b>CNS medication user; n (%)</b>	94 (31%)	53 (52%)	41 (20%)	0.0001
<b>Smoking; n (%)</b>	28 (9.2%)	12 (11.8%)	16 (7.9%)	0.26

<b>Blood pressure</b>			0.13
<b>Normal; n (%)</b>	76 (25%)	20 (20%)	56 (28%)
<b>High; n (%)</b>	166 (55%)	65 (65%)	101 (50%)
<b>Low; n (%)</b>	51 (17%)	16 (16%)	35 (17%)

Abbreviations: BMI: body mass index; CNS: central nervous system; MAP: mean arterial pressure; PP: pulse pressure. <sup>a</sup>: P value indicates comparison between dialysis and non-dialysis groups; <sup>b</sup>: indicates continuity correction; <sup>c</sup>: indicates Mann Whitney U test.

**Table 4.2 Summary of the laboratory parameters**

<b>Variable</b>	<b>Entire cohort (mean ± SD)</b>	<b>The dialysis group (mean ± SD)</b>	<b>The non- dialysis group (mean ± SD)</b>	<b>P<sup>a</sup></b>
<b>e-GFR ml/min/1.73m<sup>2</sup></b>	21 (7-41) <sup>c</sup>	6.2 ± 2.6	36.6 ± 16.3	0.0001
<b>Hb (g/L)</b>	119 ± 22.3	107 ± 20	126 ± 20	0.0001 <sup>b</sup>
<b>Hct</b>	36.3 ± 8.8	33 ± 3.7	38.1 ± 10.1	0.0001 <sup>b</sup>
<b>Albumin(g/L)</b>	34.7 ± 4.9	32 ± 5	35.9 ± 4.3	0.0001
<b>PTH (pg/ml)</b>	200 (99-475) <sup>c</sup>	635 ± 570	148 ± 118	0.0001 <sup>b</sup>
<b>Calcium<sup>d</sup> (mmol/L)</b>	2.2 ± 0.67	2.38 ± 0.18	2.11 ± 0.8	0.88 <sup>b</sup>
<b>P (mmol/L)</b>	1.4 ± 0.4	1.8 ± 0.5	1.2 ± 0.3	0.0001 <sup>b</sup>
<b>Glucose (mmol/L)</b>	6.1 (4.9-8.6) <sup>c</sup>	8.6 ± 7.5	7.1 ± 3.3	0.3 <sup>b</sup>

Abbreviations: eGFR: estimated glomerular filtration rate; Hb: hemoglobin; Hct: hematocrit; PTH: parathyroid hormone; P: phosphate. <sup>a</sup>: P value indicates comparison between dialysis and non-dialysis groups; <sup>b</sup>: Indicates Mann Whitney U test; <sup>c</sup>: Indicates median (interquartile range), <sup>d</sup>: Indicates corrected calcium.

Sleep quality was evaluated with the PSQI as categorical and continuous variables. All participants completed the survey. A total of 117 participants (39%) were labeled as poor sleepers. Among those on a dialysis treatment, 47 (47%) patients were identified as poor sleepers whereas the non-dialysis group had 70 (35%) patients with poor sleep status. The Pearson Chi-square test was employed to test the difference in frequencies between the groups. There was a statically significant difference with a higher frequency in the dialysis group (P: 0.05).

A total of 21 non-dialysis CKD respondents and 9 dialysis respondents reported that they had been diagnosed with and/or treated for sleep apnea. The Berlin Questionnaire indicated high risk for sleep apnea in 157 (51.8%) patients in the study cohort. In the dialysis group, 56 (55%) participants were classified as high-risk while in the CKD group, 101 (50%) patients indicated high-risk status for sleep apnea. The frequency was not significantly different between the groups (P: 0.37).

The BDI was used for depression screening in this study. Only two participants did not complete the survey. The tool was administered to a total of 301 respondents (mean score  $5.19 \pm 5.34$ ). A total of 13 patients were classified as depressive (10 in the dialysis group and 3 in the non-dialysis group). There was a significant difference between the groups in the prevalence of depression with the BDI (P: 0.002 with continuity correction). The BDI-FS was positive in 28 respondents (9.24%). There was also a significant difference in the prevalence of depression between the dialysis and non-dialysis groups (P: 0.005) using the BDI-FS. Thus, the dialysis group included a higher proportion of depressive

patients, according to the questionnaires. The table 4.3 summarizes the results of the questionnaires.

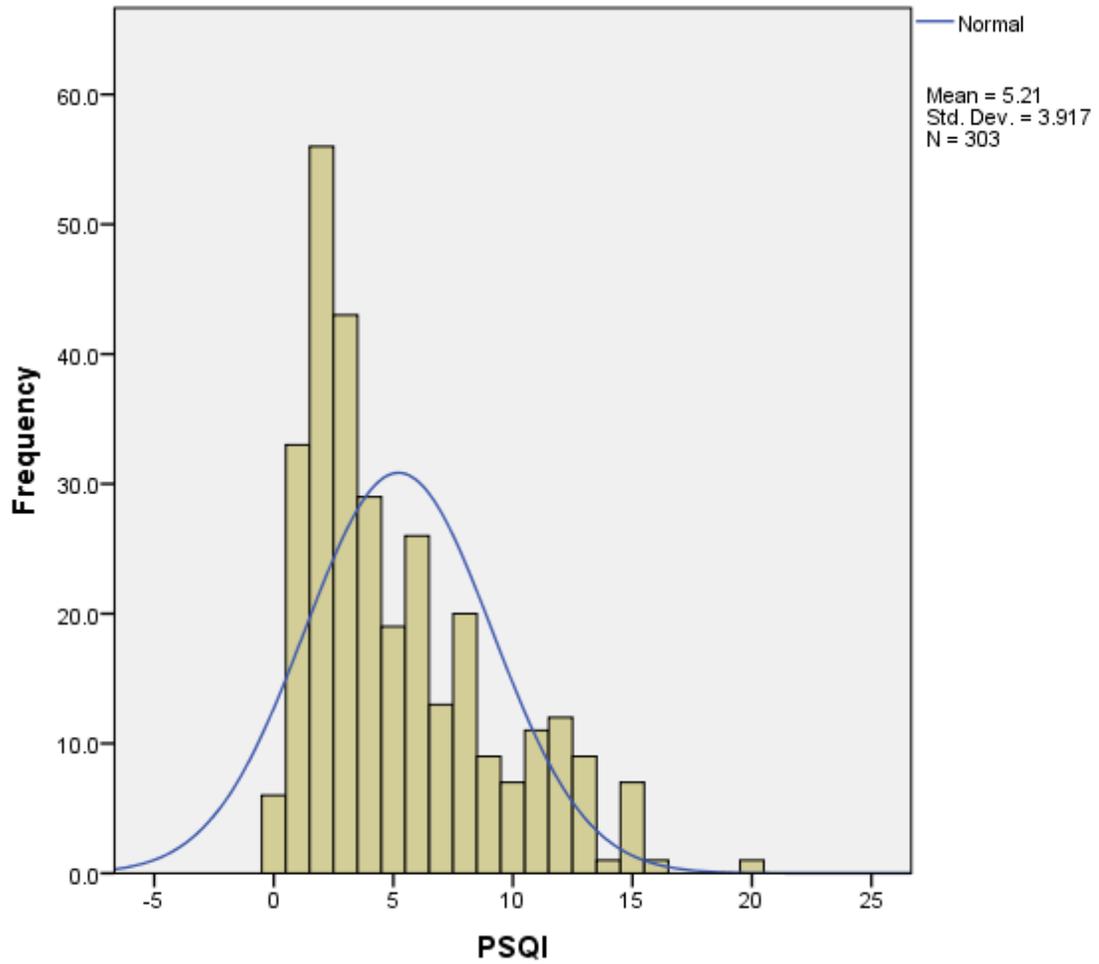
**Table 4.3 Summary of the questionnaire scores**

<b>Variable</b>	<b>Entire cohort (mean ± SD)</b>	<b>The dialysis group (mean ± SD)</b>	<b>The non-dialysis group (mean ± SD)</b>	<b>P value</b>
<b>PSQI</b>	4 (2-8) <sup>d</sup>	5.9 ± 4.2	4.9 ± 3.7	0.02
<b>BDI</b>	4 (2-7) <sup>d</sup>	7.9 ± 7.1	3.9 ± 3.5	0.0001 <sup>c</sup>
<b>BDI-FS</b>	1.07 ± 1.9	1.7 ± 2.5	0.8 ± 1.6	0.0001 <sup>c</sup>
<b>PCS</b>	42 ± 10	39.8 ± 10	43.6 ± 10.7	0.004
<b>MCS</b>	53 ± 9	49.9 ± 11	55.3 ± 7.5	0.0001 <sup>c</sup>
<b>PF</b>	46 (33-54) <sup>d</sup>	39.9 ± 11.5	45.5 ± 10.7	0.0001
<b>RP</b>	39 (30-57) <sup>d</sup>	37.9 ± 12.1	43.1 ± 13.6	0.001 <sup>c</sup>
<b>BP</b>	52 (38-62) <sup>d</sup>	49.7 ± 12.6	50.6 ± 11.4	0.53
<b>GH</b>	50 (40-55) <sup>d</sup>	45.2 ± 10.3	49.6 ± 9.8	0.0001
<b>VT</b>	47 (35-53) <sup>d</sup>	43.4 ± 11.2	44.6 ± 11	0.34
<b>SF</b>	57 (37-57) <sup>d</sup>	39.9 ± 15.1	51.1 ± 10.2	0.0001 <sup>c</sup>
<b>RE</b>	56 (46-56) <sup>d</sup>	48.8 ± 9.5	53.7 ± 5.4	0.0001 <sup>c</sup>
<b>MH</b>	58 (48-61) <sup>d</sup>	51.6 ± 11.8	55.5 ± 9.4	0.006 <sup>c</sup>
<b>Variable</b>	<b>Entire cohort N (%)</b>	<b>The dialysis group N (%)</b>	<b>The non-dialysis group N (%)</b>	<b>P value</b>
<b>PSQI categorical (score &gt;5)</b>	117 (39)	47 (47%)	70 (35%)	0.05
<b>BQ</b>	157 (51.8%)	56 (55%)	101 (50%)	0.37
<b>BDI categorical</b>	13 (4%)	10 (10%)	3 (1%)	0.002 <sup>b</sup>
<b>BDI-FS categorical</b>	28 (9%)	16 (16%)	12 (6%)	0.005

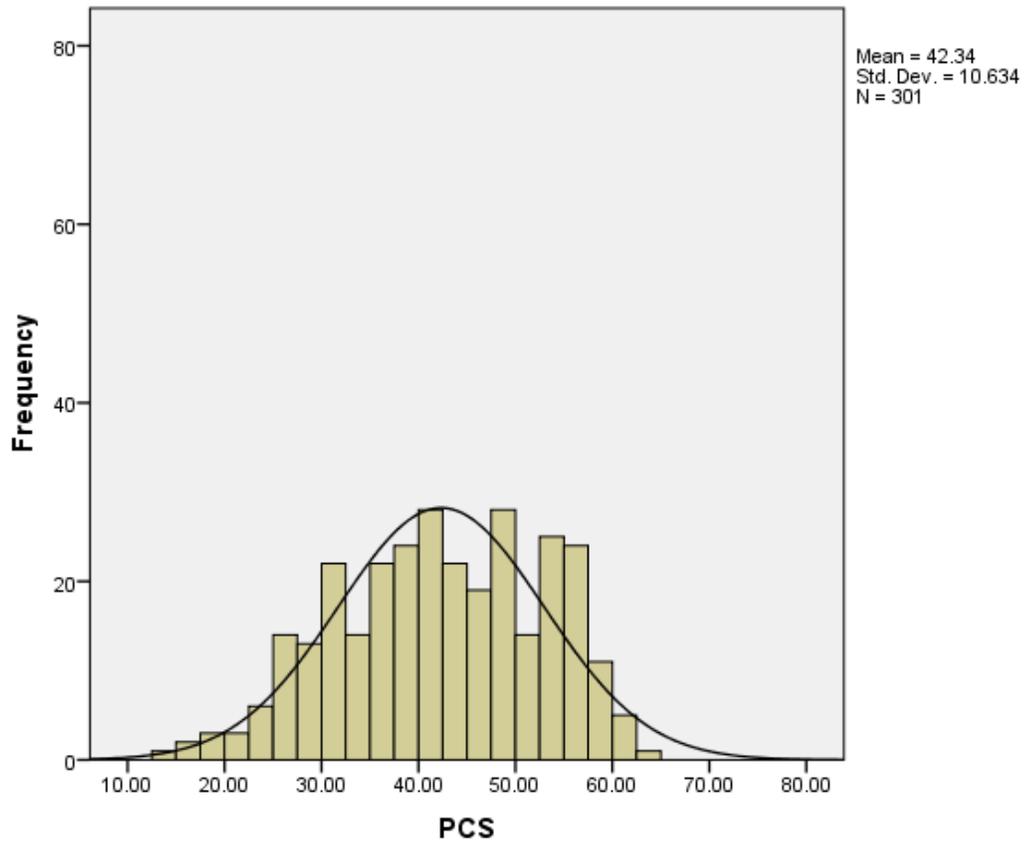
Abbreviations: BP: Bodily Pain; BQ: Berlin Questionnaire; BDI: Beck Depression Inventory; BDI-FS: Beck Depression Inventory Fast Screening; GH: General Health; MCS: Mental Component Summary; MH: Mental Health; PCS: Physical Component Summary; PF: Physical Functioning; PSQI: Pittsburgh Sleep Quality Index; RE: Role Emotional; RP: Role Physical; SF: Social Functioning VT: Vitality. <sup>b</sup>: Indicates continuity correction; <sup>c</sup>: Indicates Mann Whitney U; <sup>d</sup>: Indicates median (interquartile range).

Normalized scores from the eight scales and two summary measures of the SF-36 questionnaire are displayed in the table 4.3. Only two participants did not complete the survey. PF, RP, and VT normalized scores were lower than the general population mean of 50 in the study cohort. Additionally, PCS scores were lower while MCS scores were about the same with a normal mean of 50 ( $42 \pm 10$  versus  $53 \pm 9$  for PCS and MCS, respectively). Excluding BP and VT, all of the scores of scales were significantly lower in the dialysis group when compared to the non-dialysis group. PCS and MCS scores were also significantly lower in the dialysis group.

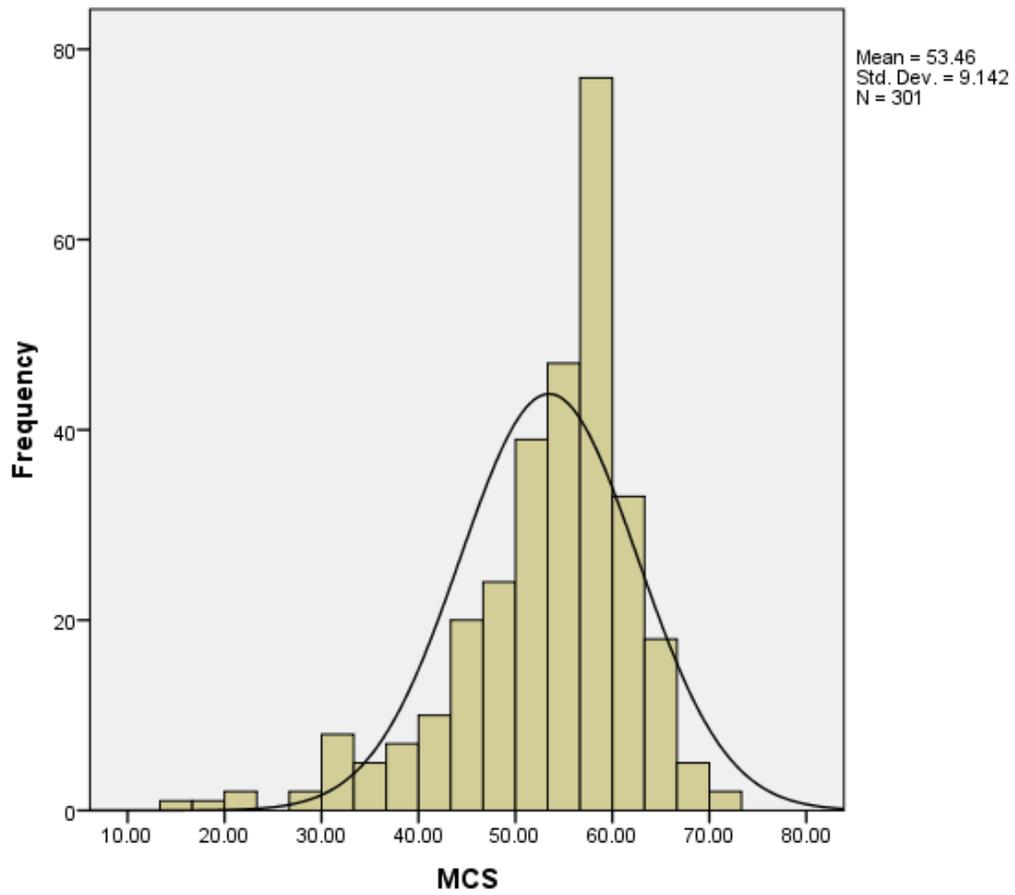
The distribution of the continuous variables was tested using histograms, and a normal curve was displayed on each graph. Median and interquartile ranges were used for non-normally distributed data, while mean and standard deviation were used in the normally distributed data. Please see the following pages for selected figures that indicate distribution of continuous variables including the PSQI, PCS, MCS, and BDI scores (figures 4.1, 4.2, 4.3, and 4.4, respectively). The PSQI and BDI scores' distributions were slightly positively skewed.



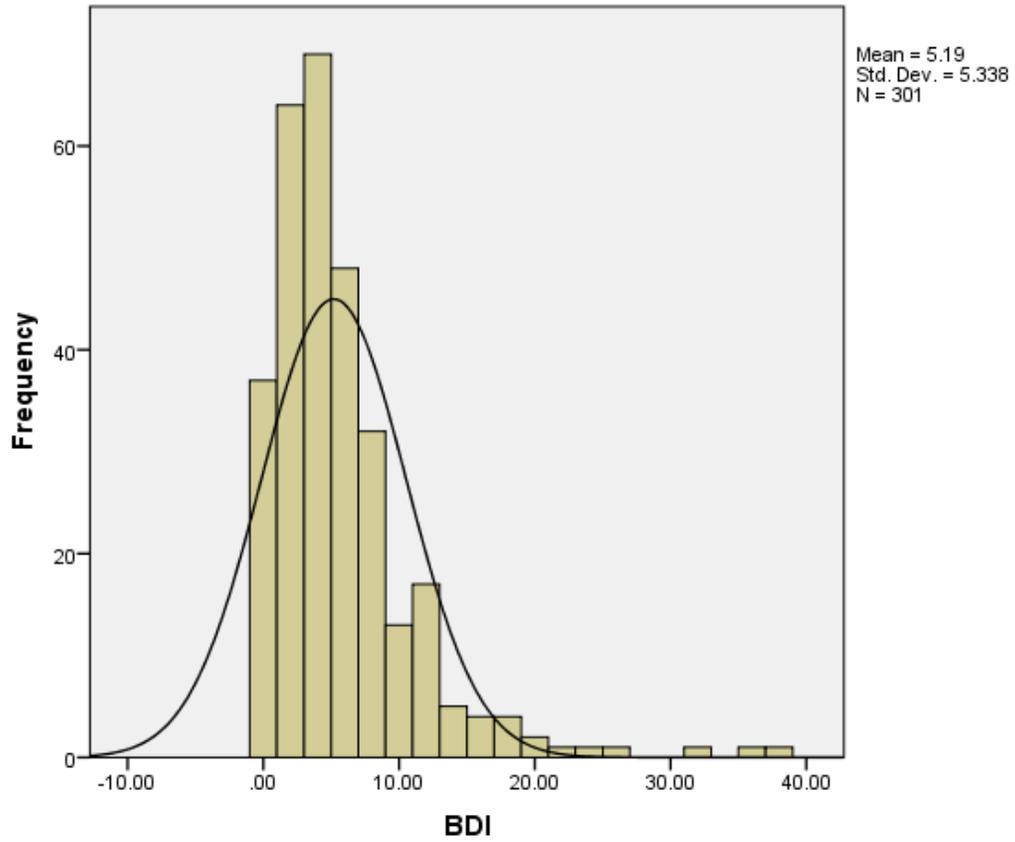
**Figure 4.1** A histogram displaying the PSQI global score distribution in the study cohort



**Figure 4.2 A histogram displaying the PCS score distribution in the study cohort**

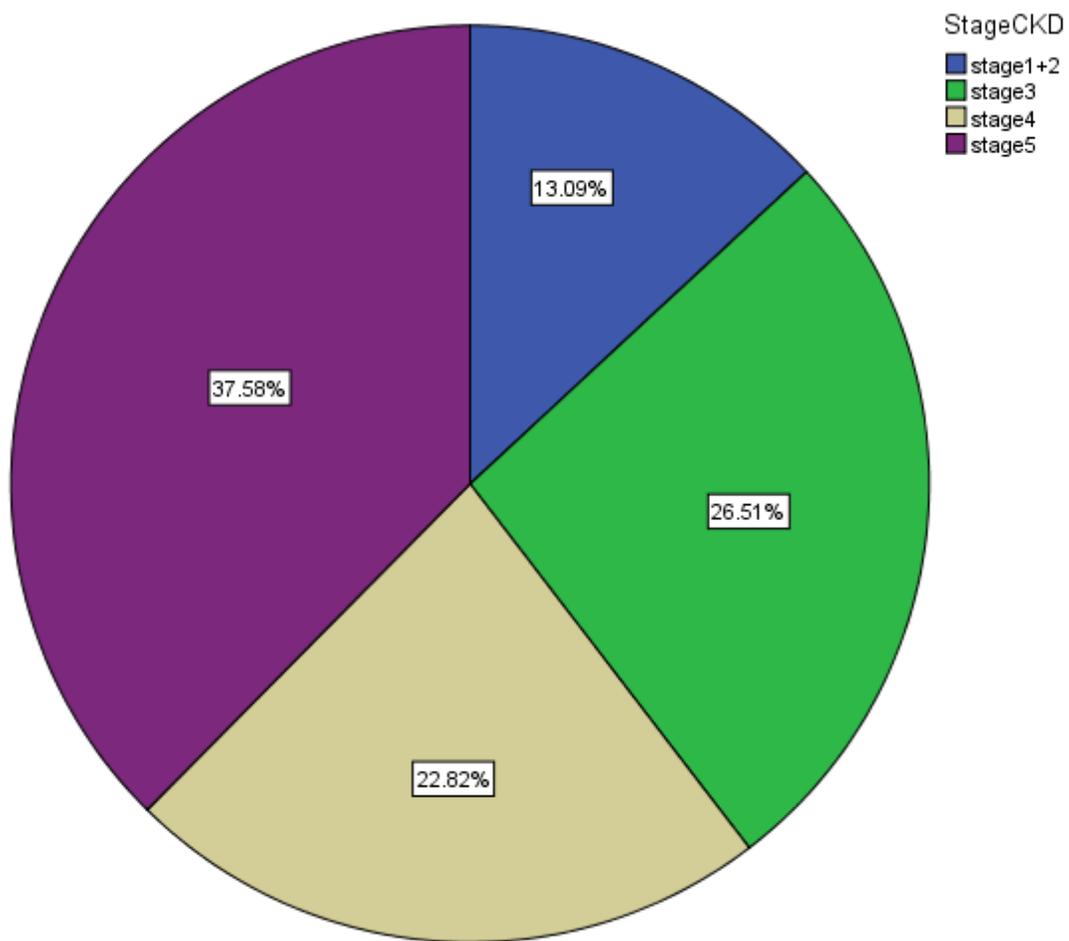


**Figure 4.3** A histogram displaying the MCS score distribution in the study cohort



**Figure 4.4** A histogram displaying the BDI score distribution in the study cohort

The distribution of CKD stages in the study cohort was also examined. The majority of the study cohort consisted of patients with stage 5 CKD (37.6%). Stage 1 and 2 were collapsed into one category and only constitute 13% of the study cohort (please see the figure 4.5).



**Figure 4.5** A pie chart displaying the stages of CKD in the study cohort

## **4.2 Correlation Analyses**

Correlations of sleep quality, sleep apnea, depression, and quality of life with covariates were performed.

### **4.2.1 Associations for Sleep Quality**

Impaired sleep was more common in females (P: 0.0001). Those who were married or had a common-law partner were less likely to have a poor sleep quality (P: 0.01). High risk for sleep apnea was significantly higher in those with poor sleep quality (P: 0.02). Patients with depression were more likely to have a poor sleep quality, whereas those with good sleep quality had significantly higher MCS scores. PCS scores were slightly higher in the good sleepers, but did not reach a statistically significant level (P: 0.07). Please see table 4.4 for complete results.

**Table 4.4 Associations between sleep quality and covariates**

<b>Variable</b>	<b>PSQI global score <math>\geq</math> 5</b>	<b>PSQI global score <math>&lt;</math> 5</b>	<b>P value</b>
<b>Age (mean <math>\pm</math>SD)</b>	63.2 $\pm$ 14.9	62.3 $\pm$ 14.2	0.6
<b>Gender (female); n (%)</b>	65 (55%)	60 (32%)	0.0001
<b>Married or common law partner; n (%)</b>	59 (58%)	127 (73%)	0.01
<b>BMI (Kg/m<sup>2</sup>) (mean <math>\pm</math> SD)</b>	29.7 $\pm$ 7.2	29.8 $\pm$ 5.8	0.9
<b>Diabetes positive; n (%)</b>	57 (48%)	84 (45%)	0.5
<b>Current smokers; n (%)</b>	14 (12%)	14 (7%)	0.19
<b>Blood pressure</b>			0.13
<b>Controlled (number, %)</b>	32 (28%)	44 (25%)	
<b>High (number, %)</b>	57 (50%)	109 (61%)	
<b>Low (number, %)</b>	25 (22%)	26 (15%)	
<b>MAP mmHg (mean <math>\pm</math>SD)</b>	91.2 $\pm$ 15.3	91.4 $\pm$ 12.1	0.6
<b>PP mmHg (mean <math>\pm</math>SD)</b>	71.7 $\pm$ 23.7	72.8 $\pm$ 20	0.7
<b>Hb g/L (mean <math>\pm</math>SD)</b>	119.2 $\pm$ 18	122 $\pm$ 19	0.2
<b>eGFR ml/min/1.73 m<sup>2</sup> (mean <math>\pm</math>SD)</b>	24.8 $\pm$ 20.6	27.2 $\pm$ 19	0.3
<b>Stage of CKD</b>			0.11
<b>Stage1+2 (number, %)</b>	17 (15%)	22 (12%)	
<b>Stage3 (number, %)</b>	25 (22%)	54 (29%)	
<b>Stage4 (number, %)</b>	21 (18%)	47 (26%)	
<b>Stage5 (number, %)</b>	51 (45%)	61 (33%)	
<b>BQ high risk; n (%)</b>	70 (60%)	87 (47%)	0.02
<b>BDI (mean <math>\pm</math>SD)</b>	7.1 $\pm$ 6.9	3.9 $\pm$ 3.4	0.0001
<b>BDI-FS (mean <math>\pm</math>SD)</b>	1.5 $\pm$ 2.5	0.7 $\pm$ 1.4	0.0001
<b>PCS (mean <math>\pm</math>SD)</b>	40.9 $\pm$ 10.1	43.1 $\pm$ 10.8	0.07
<b>MCS (mean <math>\pm</math>SD)</b>	50.1 $\pm$ 10.3	55.5 $\pm$ 7.6	0.0001 <sup>a</sup>

Abbreviations: BQ: Berlin Questionnaire; BDI: Beck Depression Inventory; BDI-FS: the Beck Depression Inventory Fast Screening BMI: body mass index; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; Hb: hemoglobin; MAP: mean arterial pressure; MCS: Mental Component Summary; PP: pulse pressure; PCS: Physical Component Summary; PSQI: the Pittsburgh Sleep Quality Index. <sup>a</sup>: indicates Mann Whitney U test.

### **4.2.2 Associations for Sleep Apnea**

Those with a high risk for sleep apnea were younger and had a higher BMI and MAP values (P: 0.02 for age, P: 0.0001 for BMI, and P: 0.01 for MAP). Patients with depression and poor sleep quality were also more likely to be in the high risk category for sleep apnea. High risk for sleep apnea was also associated with low PCS and MCS domain scores. Please see table 4.5 for details.

**Table 4.5 Associations between sleep apnea and covariates**

<b>Variable</b>	<b>High risk for sleep apnea</b>	<b>Low risk for sleep apnea</b>	<b>P value</b>
<b>Age (mean ± SD)</b>	60.7 ± 13.3	64.7 ± 15.4	0.02
<b>Gender (female); n (%)</b>	61 (38%)	64 (44%)	0.3
<b>Married or common law partner; n (%)</b>	97 (70%)	89 (65%)	0.4
<b>BMI (Kg/m<sup>2</sup>) (mean ± SD)</b>	31.4 ± 7.1	28.1 ± 5.1	0.0001 <sup>a</sup>
<b>Diabetes positive; n (%)</b>	78 (50%)	63 (43%)	0.2
<b>Current smokers</b>	15 (9%)	13 (9%)	0.8
<b>Blood pressure</b>			0.3
<b>Controlled; n (%)</b>	38 (25%)	38 (27%)	
<b>High; n (%)</b>	94 (60%)	72 (52%)	
<b>Low; n (%)</b>	23 (15%)	28 (20%)	
<b>MAP (mean ± SD)</b>	93.2 ± 13.3	89.2 ± 13.2	0.01
<b>PP (mean ± SD)</b>	73.5 ± 22.7	71.1 ± 20.1	0.3
<b>Hb (mean ± SD)</b>	120.9 ± 19.4	121.2 ± 18.3	0.9
<b>eGFR (mean ± SD)</b>	25.9 ± 19.9	26.7 ± 19.4	0.8
<b>Stage of CKD</b>			0.3
<b>Stage1+2; n (%)</b>	22 (14%)	17 (12%)	
<b>Stage3; n (%)</b>	34 (22%)	45 (31%)	
<b>Stage4; n (%)</b>	38 (25%)	30 (21%)	
<b>Stage5; n (%)</b>	61 (39%)	51 (36%)	
<b>PSQI (mean ± SD)</b>	5.9 ± 4.1	4.4 ± 3.5	0.001 <sup>a</sup>
<b>BDI (mean ±SD)</b>	6.2 ± 5.7	4.1 ± 4.5	0.001
<b>BDI-FS (mean ± SD)</b>	1.4 ± 2.2	0.6 ± 1.4	0.0001 <sup>a</sup>
<b>PCS (mean ± SD)</b>	41.1 ± 10	43.5 ± 11.1	0.05
<b>MCS (mean ± SD)</b>	51.2 ± 9.7	55.7 ± 7.8	0.0001 <sup>a</sup>

Abbreviations: BDI: the Beck Depression Inventory; BDI-FS: the Beck Depression Inventory Fast Screening; BMI: body mass index; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; Hb: hemoglobin; MAP: mean arterial pressure; MCS: Mental Component Summary; PCS: Physical Component Summary; PP: pulse pressure; PSQI: the Pittsburgh Sleep Quality Index. <sup>a</sup>: indicates Mann Whitney U test.

### **4.2.3 Associations for Depression**

Depression was associated with younger age and female gender (P: 0.01 for age and P: 0.01 for gender). Advanced kidney disease and poor sleep quality were also associated with depression (P: 0.005 for eGFR, P: 0.02 for stage of CKD, and P: 0.0001 for sleep quality). MCS scores were significantly higher in the non-depressive patients ( $33.7 \pm 11.5$  for depressive group and  $54.4 \pm 7.8$  for non-depressive group, P: 0.0001). Diabetes mellitus and PCS clearly differed, but did not reach significance level due to power. Please see table 4.6 for details.

**Table 4.6 Association between depression and covariates**

<b>Variable</b>	<b>Depression positive</b>	<b>Depression negative</b>	<b>P value</b>
<b>Age (mean ±SD)</b>	53 ± 16	63 ± 14	0.01
<b>Gender (female); n (%)</b>	10 (77%)	115 (40%)	0.01 <sup>b</sup>
<b>Married or common law partner; n (%)</b>	7 (58%)	178 (68%)	0.6 <sup>b</sup>
<b>BMI (Kg/m<sup>2</sup>); (mean ±SD)</b>	26.9 ± 6.9	29.9 ± 6.3	0.1
<b>Diabetes positive; n (%)</b>	8 (61%)	132 (46%)	0.4 <sup>b</sup>
<b>Current smokers; n (%)</b>	3 (23%)	25 (9%)	0.2 <sup>b</sup>
<b>Blood pressure</b>			0.9 <sup>c</sup>
<b>Control; n (%)</b>	3 (23%)	73 (26%)	
<b>High; n (%)</b>	8 (62%)	156 (56%)	
<b>Low; n (%)</b>	2 (15%)	49 (18%)	
<b>MAP (mean ±SD)</b>	97.9 ± 21.05	91 ± 12.9	0.3 <sup>a</sup>
<b>PP (mean ±SD)</b>	70.8 ± 18.7	72.5 ± 21.7	0.7
<b>Hb (mean ±SD)</b>	133.9 ± 14.8	132.4 ± 15.4	0.7
<b>eGFR (mean ±SD)</b>	11 ± 7.5	27 ± 19.8	0.005 <sup>a</sup>
<b>Stage of CKD</b>			0.02 <sup>c</sup>
<b>Stage1+2; n (%)</b>	0 (0%)	39 (14%)	
<b>Stage3; n (%)</b>	0 (0%)	79 (28%)	
<b>Stage4; n (%)</b>	3 (23%)	64 (23%)	
<b>Stage5; n (%)</b>	10 (77%)	101 (36%)	
<b>PSQI (mean ±SD)</b>	10.6 ± 3.8	4.9 ± 3.7	0.0001
<b>BQ positive</b>	11 (85%)	145 (50%)	0.03 <sup>b</sup>
<b>BDI-FS positive</b>	12 (90%)	16 (5%)	0.0001 <sup>b</sup>
<b>PCS (mean ±SD)</b>	37.6 ± 10.6	42.6 ± 10.5	0.09
<b>MCS (mean ±SD)</b>	33.7 ± 11.5	54.4 ± 7.8	0.0001 <sup>a</sup>

Abbreviations: BDI-FS: Beck Depression Inventory Fast Screening; BQ: The Berlin Questionnaire; BMI: body mass index; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; Hb: hemoglobin; MAP: mean arterial pressure; MCS: Mental Component Summary; PCS: Physical Component Summary; PP: pulse pressure, PSQI: Pittsburgh Sleep Quality Index. <sup>a</sup>: indicates Mann Whitney U test; <sup>b</sup>: indicates Continuity Correction; <sup>c</sup>: indicates Likelihood Ratio.

#### 4.2.4 Associations for Summary Measures of SF-36

PCS and MCS were tested for association with various covariates using the Spearman's coefficient of correlation (r values are in tables 4.7 and 4.8). Age, BMI, PP, the PSQI global scores, the BDI scores, and the BDI-FS scores were negatively correlated with the PCS scores. Further, Hb, eGFR, and MCS scores were positively correlated with the PCS scores. MAP did not show any significant correlation with PCS scores. Please see table 4.7 and 4.8 for details.

**Table 4.7 Associations for PCS and covariates**

<b>Variable</b>	<b>r</b>	<b>P value</b>
<b>Age</b>	-0.24	0.0001
<b>BMI</b>	-0.15	0.009
<b>MAP</b>	0.02	0.7
<b>PP</b>	-0.14	0.01
<b>Hb</b>	0.32	0.0001
<b>eGFR</b>	0.20	0.001
<b>PSQI</b>	-0.16	0.006
<b>BQ</b>	-0.12	0.02
<b>BDI</b>	-0.47	0.0001
<b>BDI-FS</b>	-0.26	0.0001
<b>MCS</b>	0.60	0.03

Abbreviations: BQ: Berlin Questionnaire; BDI: Beck Depression Inventory; BDI-FS: Beck Depression Inventory Fast Screening; BMI: body mass index; eGFR: estimated glomerular filtration rate; Hb: hemoglobin; MAP: mean arterial pressure; MCS: Mental Component Summary; PCS: Physical Component Summary; PP: pulse pressure; PSQI: Pittsburgh Sleep Quality Index.

Age, Hb, and eGFR were positively correlated with MCS scores (r: 0.14, P: 0.01 for age; r: 0.11, P: 0.04 for Hb; r: 0.19, P: 0.001 for eGFR). MAP, PSQI, BDI, and BDI-FS were negatively correlated with MCS scores. BMI and PP did not reach a significant level (P: 0.77 for BMI and P: 0.82 for PP).

**Table 4.8 Associations for MCS and covariates**

<b>Variable</b>	<b>r</b>	<b>P value</b>
<b>Age</b>	0.14	0.01
<b>BMI</b>	-0.01	0.77
<b>MAP</b>	-0.13	0.02
<b>PP</b>	0.01	0.82
<b>Hb</b>	0.11	0.04
<b>eGFR</b>	0.19	0.001
<b>PSQI</b>	-0.28	0.0001
<b>BQ</b>	-0.26	0.0001
<b>BDI</b>	-0.52	0.0001
<b>BDI-FS</b>	-0.55	0.0001
<b>PCS</b>	0.03	0.6

Abbreviations: BQ: Berlin Questionnaire; BDI: Beck Depression Inventory; BDI-FS: Beck Depression Inventory Fast Screening; BMI: body mass index; eGFR: estimated glomerular filtration rate; Hb: hemoglobin; MAP: mean arterial pressure; MCS: Mental Component Summary; PCS: Physical Component Summary; PP: pulse pressure; PSQI: Pittsburgh Sleep Quality Index.

### **4.3 Inferential Statistics:**

#### **4.3.1 Univariate Analysis**

Univariate analysis was performed as well as multivariate analysis, some of which were reduced models. The enter method was used for selecting variables. The outcome variable was sleep quality as determined by the PSQI score. Each step was tested for goodness of fit with 95% confidence intervals (CI).

Univariate analysis was performed for each predictor variable, including age, gender, BMI, presence of diabetes, smoking, hemoglobin, stages of CKD, SBP, DBP, MAP, PP, CNS medication use, achievement of blood pressure control, dialysis treatment, eGFR, BDI, BQ, PCS, and MCS scores. The significance level was 0.1 for retention in the multivariate models. Age, BMI, presence of diabetes mellitus, current smoker status, stage of CKD, SBP, DBP, MAP, PP, blood pressure control status, hemoglobin, and eGFR were not significantly associated with sleep quality ( $P > 0.1$ ). Thus, those factors were excluded from the multivariate analysis. In the univariate models, gender, CNS medication use, dialysis treatment, and BDI, BQ, PCS, and MCS scores reached a significant level of 0.1, and those covariates were included in the multivariate analysis (please see table 4.9 for the univariate analysis and table 4.11 for the multivariate analysis).

**Table 4.9 The summary of univariate analysis for sleep quality**

<b>Variables<sup>a</sup></b>	<b>Exp (B)</b>	<b>95% CI</b>	<b>P value</b>
<b>Age</b>	1.004	0.98–1.02	0.59
<b>Gender<sup>b</sup></b>	2.6	1.6–4.2	0.0001
<b>BMI (Kg/m<sup>2</sup>)</b>	0.99	0.96–1.03	0.88
<b>Diabetes<sup>c</sup></b>	1.14	0.72–1.82	0.57
<b>Current smokers</b>	1.67	0.77–3.6	0.19
<b>Hb</b>	0.99	0.97–1	0.21
<b>Stages of CKD</b>	1.12	0.9–1.4	0.3
<b>SBP</b>	0.99	0.98–1	0.7
<b>DBP</b>	1	0.98–1	0.8
<b>MAP</b>	0.99	0.98–1.01	0.86
<b>PP</b>	0.99	0.98–1.00	0.67
<b>CNS medication users<sup>d</sup></b>	0.29	0.18–0.495	0.0001
<b>Blood pressure</b>			
<b>High</b>	0.72	0.41–1.2	0.24
<b>Low</b>	1.3	0.6–2.6	0.44
<b>Dialysis<sup>e</sup></b>	1.64	1.1–2.7	0.04
<b>eGFR</b>	0.99	0.98–1.006	0.28
<b>BDI</b>	1.14	1.1–1.2	0.0001
<b>BQ<sup>f</sup></b>	1.69	1.06–2.7	0.02
<b>PCS</b>	0.98	0.96–1.003	0.08
<b>MCS</b>	0.93	0.90–0.96	0.0001

Abbreviations: BQ: Berlin Questionnaire; BDI: Beck Depression Inventory; BDI-FS: Beck Depression Inventory Fast Screening; BMI: body mass index; CKD: chronic kidney disease; CNS: central nervous system; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate; Hb: hemoglobin; MAP: mean arterial pressure; MCS: Mental Component Summary; PCS: Physical Component Summary; PP: pulse pressure; SBP: systolic blood pressure. <sup>a</sup>: Logistic regression with enter method (P: 0.05) was performed to identify factors independently associated with sleep quality in the study cohort; <sup>b</sup>: Indicator female gender; <sup>c</sup>: Indicator presence of diabetes; <sup>d</sup>: Indicator use of CNS medication; <sup>e</sup>: Indicator receiving a dialysis treatment; <sup>f</sup>: Indicator a positive result from the BQ.

### 4.3.2 Multivariate Analyses

Firstly, the overall model fit was tested. The hypothesis was stated as follows:

**Table 4.10 Statements of the Null and Alternative Hypothesis**

$H_0^a = B_1 = B_2 = B_3 \dots = 0$
$H_a^b = \text{At least one } B_{xc} \neq 0$

<sup>a</sup>: Indicates the Null hypothesis; <sup>b</sup>: Indicates the Alternative hypothesis; <sup>c</sup>: Indicates any possible predictor being tested.

The Wald chi-square test was significant in the null model, indicating that this model was better than no model at all. Since the Wald test has been associated with a risk for type 2 error, model fit was also evaluated by additional tests. However, type 2 error is the risk for a non-significant result when in fact an association exists. Since we had a significant result, type 2 error risk did not exist in our models. The goodness of fit was also tested by the Omnibus test, Hosmer-Lemeshow test, as well as Cox-Snell  $R^2$  and Nagelkarke  $R^2$  values (P: 0.0001 for the Omnibus test, P: 0.68 for the Hosmer-Lemeshow test). Both P values supported model fit. The Hosmer-Lemeshow is considered most reliable in the presence of one predictor for every ten observations. In this analysis, the main outcome was sleep quality, and a total of 117 patients had poor sleep quality. The model could accommodate 11–12 predictors according to the rule. In the multivariate model, only seven predictors were tested.

Cox-Snell  $R^2$  and Nagelkarke  $R^2$  values were used, neither of which reached one. The former was 0.17, and the latter was 0.23. Both values implied some correlation, but not a perfect fit.

Individual predictors were also tested by the Wald test. The multivariate analysis (please see table 4.11) did not reach a significant level ( $P < 0.05$ ) for receiving dialysis treatment, depression, sleep apnea, and PCS scores. Subsequently, those were excluded in the reduced model.

C index was 61.5% in step 0 and 68.6% in step 1. Predictive power of the model was increased by adding predictors, as the C index was improved by 7.1%. This increase was substantial and implied that at least one predictor had a strong association with the outcome variable. The ideal C-index is 100%, while the minimum acceptable limit is 50%.

To conclude, the results of the multivariate analyses indicated that CNS medication use was associated with a higher risk for having poor sleep quality (OR: 2.6, 95% CI: 1.4–4.9, P: 0.002 for CNS medication use). Being a female was associated with a 2.5-fold increase in risk for having poor sleep quality (OR: 2.5, 95% CI: 1.5–4.3, P: 0.0001). Having high MCS scores was tied to having a higher sleep quality.

**Table 4.11 The Summary of multivariate analysis for sleep quality**

Variables <sup>h</sup>	Exp (B)	95% CI	P value
<b>Gender<sup>a</sup></b>	2.5	1.5–4.3	0.0001
<b>CNS meds users<sup>b</sup></b>	2.6	1.4–4.9	0.002
<b>Dialysis<sup>c</sup></b>	0.99	0.5–1.8	0.99
<b>BDI</b>	1.1	0.98–1.14	0.1
<b>BQ<sup>d</sup></b>	1.3	0.8–2.3	0.2
<b>PCS</b>	1	0.9–1.02	0.90
<b>MCS</b>			0.06
<b>Category (1)<sup>e</sup></b>	1.3	0.6–2.8	0.45
<b>Category (2)<sup>f</sup></b>	0.8	0.4–1.6	0.58
<b>Category (3)<sup>g</sup></b>	0.4	0.2–0.8	0.01

Abbreviations: BQ: Berlin Questionnaire; BDI: Beck Depression Inventory; CNS: central nervous system; MCS: Mental Component Summary; PCS: Physical Component Summary. <sup>a</sup>: Indicator female gender; <sup>b</sup>: Indicator CNS medication use; <sup>c</sup>: Indicator receiving dialysis treatment; <sup>d</sup>: Indicator positive Berlin Questionnaire; <sup>e</sup>: Indicates comparison of less than 25%percentile with 25-50% percentile categories; <sup>f</sup>: Indicates comparison of 25-50% percentile with 50-75% percentile categories; <sup>g</sup>: Indicates comparison of 50-75% percentile with more than 75% percentile categories; <sup>h</sup>:Logistic regression with enter method (P: 0.05) was performed to identify factors independently associated with sleep quality in the study cohort.

The reduced models included gender, CNS medication use, and MCS scores. Female gender increases the risk for poor sleep quality, whereas high MCS domain scores and not receiving a CNS medication reduces the risk for impaired sleep. -2log likelihood values were registered to compare the full model with the reduced model. It is known that the value should decrease to justify a better model in the same dataset. -2log likelihood in the

multivariate analysis was 342, while it was 348.8 in the reduced model. There was a minimal increase, which might be neglected.

**Table 4.12 The Summary of reduced models for sleep quality**

<b>Variables<sup>a</sup></b>	<b>Exp (B)</b>	<b>95% CI</b>	<b>P value</b>
<b>Gender<sup>b</sup></b>	2.6	1.5-4.3	0.0001
<b>CNS medication users<sup>c</sup></b>	3.1	1.8-5.5	0.0001
<b>MCS</b>			0.003
<b>Category (1)<sup>d</sup></b>	1.03	0.5-2	0.9
<b>Category (2)<sup>e</sup></b>	0.6	0.3-1.2	0.1
<b>Category (3)<sup>f</sup></b>	0.3	0.2-0.6	0.001

Abbreviations: CNS: central nervous system; MCS: mental summary scale. <sup>a</sup>: Logistic regression with enter method (P: 0.05) was performed to identify factors independently associated with sleep quality in the study cohort; <sup>b</sup>: Indicator female gender; <sup>c</sup>: Indicator using a CNS medication; <sup>d</sup>: Indicates comparison of less than 25% percentile with 25-50% percentile categories; <sup>e</sup>: Indicates comparison of 25-50% percentile with 50-75% percentile categories; <sup>f</sup>: Indicates comparison of 50-75% percentile with more than 75% percentile categories.

### **4.3.3 Assumptions**

Finally, assumptions for the logistic regression were tested followed by the residual analysis. A sample was used to make an inference for the population. As a result, assumptions were needed to be met to generalize the results of the study. Several assumptions have been tested, including independence, linearity, and multicollinearity.

#### **4.3.3.1 Independence**

Independence of sample observations was met since it was a random sampling; therefore, the observed relationship may be generalizable. Nevertheless, dispersion was also tested to prove the independence of the observations.

#### **4.3.3.2 Linearity**

Log odds of success are the linear function of the outcome variable. PCS and MCS scores were two continuous variables that were included in the multivariate analysis. The interactions of the aforementioned continuous variables with logarithmic transformation of PCS and MCS values were used to test the linearity assumption with a critical P value of 0.05. PCS and log of PCS interaction indicated a P value of 0.07, thus, the assumption was not violated for PCS scores. However, the interaction for MCS scores was associated with a P value of 0.0001. As a result, the assumption was violated for MCS scores.

There are two methods that might be used when the linearity assumption is violated: transforming metric variables to ordinal level or categorization and inter-category comparison. We used the second approach, as previously mentioned. MCS was

categorized into quartiles (25%, 50%, 75%, and 100%), and included in the multivariate models as a categorical variable. A difference method was used to compare categories. Please see the following pages for the summary of the results for the linearity assumption.

**Table 4.13 The linearity assumption for PCS and MCS**

	<b>Exp(B)</b>	<b>P value</b>
<b>PCS by log</b>	.996	.075
<b>PCS</b>		
<b>MCS by</b>	.986	.000
<b>log MCS</b>		

Abbreviations: log: logarithmic transformation of the PCS scores.

### 4.3.3.3 Multicollinearity

The linear regression model was used to generate collinearity statistics. Tolerance and variance inflation factor (VIF) were used to test the assumption. Values less than 10 for VIF, and more than 0.1 for tolerance were considered violations. All of the values were below the limits. Please see the table 4.15 for collinearity statistics. Since multicollinearity was not violated, predictor variables did not have significant correlation with each other.

**Table 4.14 The Summary of collinearity statistics**

	<b>Tolerance</b>	<b>VIF</b>
<b>Gender</b>	0.96	1.03
<b>Dialysis treatment</b>	0.81	1.23
<b>CNS medication</b>	0.76	1.3
<b>BDI</b>	0.57	1.77
<b>BQ high risk</b>	0.91	1.09
<b>PCS</b>	0.83	1.19
<b>MCS</b>	0.69	1.43

Abbreviations: BDI: Beck Depression Inventory; BQ: Berlin Questionnaire; CNS: central nervous system; MCS: Mental Component Summary; PCS: Physical Component Summary; VIF: Variance Inflation Factor.

#### **4.3.4 Other Considerations Regarding the Logistic Regression**

##### **4.3.4.1 Incomplete Information**

Cross tabulation was performed with the PSQI categories and all categorical predictors, in order to evaluate the number of observations in the each cell. The assumption of “only less than 20% of cells may have less than five observations” was tested, and met. Only 1 cell had less than 5 observations, and it was the race category.

##### **4.3.4.2 Complete Separation**

This assumption was not tested as no explanatory variable was considered as a perfect predictor.

##### **4.3.4.3 Dispersion**

A multinomial logistic regression test was employed to calculate the Pearson’s chi-square goodness of fit and Deviance chi-square goodness of fit. The aforementioned tests are used to test independence. Values more than two signify over-dispersion while less than one indicates under-dispersion. In general, 1 is considered as the ideal value and shows that the model has no dispersion. Additionally, it indicates that no important covariate is missing and variables are not correlated.

In our sample, we have found 1.02 and 1.18, using Pearson’s and Deviance methods, respectively. In our models, the assumption was not violated and coefficient estimates were stable. Please see the following page for the summary of the results for that assumption.

The Pearson chi-square goodness of fit

$$\phi_{\text{Pearson}} = \sqrt{\chi^2_{\text{Pearson}} \div df} = 296 \div 288 = 1.02$$

The Deviance chi-square goodness of fit

$$\phi_{\text{Deviance}} = \sqrt{X^2_{\text{Deviance}} \div df} = 342 \div 288 = 1.18$$

**Table 4.15 Pearson's and Deviance Chi<sup>2</sup> Tests: Assumption for independence**

	Chi-Square	Degree of freedom	P value
<b>Pearson</b>	296.939	288	0.346
<b>Deviance</b>	342.108	288	0.016

### 4.3.5 Residual Analysis

An examination was made for outliers and leverage points to eliminate the possibility of the presence of unusual observations and influential data.

#### 4.3.5.1 Outliers

Standardized residuals for outliers were performed. As a rule, a maximum of 5% of the sample size may be higher than 2 (5% of 303: 15.15 cases might be higher than 2). Case-wise statistics for standardized residuals indicated 4 cases were higher than 2. Those records were rechecked for any mistake during data entry. Then, the second rule was tested: a maximum of 1% of the sample size may be more than 2.5. Only 3 cases could be

more than 2.5; however, none of the cases were more than 2.5. As a result, both assumptions were met.

#### **4.3.5.1 Leverage Points**

Cook's distances for leverage points were also analyzed. A Cook's distance value of more than 1 was considered as points that carried leverage points. Neither the Cook's distance values, nor DF-Beta values, exceeded one.

#### **4.4 Subgroup Analyses**

The study cohort included the dialysis and non-dialysis groups. Each group was tested for associations between sleep quality and risk for sleep apnea, depression, quality of life, and covariates, including age, gender, BMI, diabetes, smoking, MAP, PP, blood pressure categories, Hb, albumin, PTH, Ca, and P. Dialysis vintage in days and interdialytic weight gain were also included as covariates in the dialysis group, while eGFR was tested as a covariate in the non-dialysis group.

Of a total of 101 dialysis patients, 39 (39%) were female and 61 (61%) were male with a mean age of  $60.5 \pm 14.4$ . In the dialysis group, a total of 48 (48%) patients were poor sleepers, while a total of 56 (56%) patients had a high risk for sleep apnea, according to the BQ results. Those with poor sleep quality were more likely to be female and depressive. Further, MCS scores were significantly lower in the patients with impaired sleep. Please see the table 4.17 for the associations for sleep quality in the dialysis group.

**Table 4.16 Baseline characteristics of patients divided by sleep quality in the dialysis group**

Variables	Entire cohort	PSQI global score $\geq 5$	PSQI global score $< 5$	P value
<b>N; n (%)</b>	101	48 (48%)	53 (52%)	
<b>Age; mean <math>\pm</math>SD</b>	60.5 $\pm$ 14.4	59 $\pm$ 15	61 $\pm$ 13	0.4
<b>Gender (female); n (%)</b>	39 (39%)	24 (50%)	15 (28%)	0.02
<b>BMI (kg/m<sup>2</sup>); mean <math>\pm</math>SD</b>	29 $\pm$ 5	28 $\pm$ 5	29 $\pm$ 6	0.4
<b>Diabetes positive; n (%)</b>	53 (53%)	26 (54%)	27 (51%)	0.7
<b>Current smokers; n (%)</b>	18 (18%)	10 (21%)	8 (15%)	0.4 <sup>a</sup>
<b>MAP (mmHg); mean <math>\pm</math>SD</b>	94 $\pm$ 16	95 $\pm$ 17	93 $\pm$ 15	0.5
<b>PP (mmHg); mean <math>\pm</math>SD</b>	76 $\pm$ 23	74 $\pm$ 22	77 $\pm$ 24	0.6
<b>Blood pressure</b>				0.08 <sup>b</sup>
<b>Normal; n (%)</b>	28 (28%)	18 (37%)	10 (18%)	
<b>High; n (%)</b>	66 (66%)	28 (58%)	38 (72%)	
<b>Low; n (%)</b>	7 (7%)	2 (4%)	5 (9%)	
<b>Vintage(days); mean <math>\pm</math>SD</b>	1009 $\pm$ 952	979 $\pm$ 1012	1035 $\pm$ 904	0.8
<b>IWG (ml); mean <math>\pm</math>SD</b>	1751 $\pm$ 827	1701 $\pm$ 1007	1727 $\pm$ 642	0.7
<b>Hb; mean <math>\pm</math>SD</b>	107 $\pm$ 20	106 $\pm$ 22	107 $\pm$ 18	0.9
<b>Albumin; mean <math>\pm</math>SD</b>	32 $\pm$ 5	32 $\pm$ 4	32 $\pm$ 5	0.9
<b>PTH; mean <math>\pm</math>SD</b>	635 $\pm$ 570	635 $\pm$ 534	635 $\pm$ 606	0.9
<b>Calcium<sup>d</sup>; mean <math>\pm</math>SD</b>	2.2 $\pm$ 0.67	2.4 $\pm$ 0.2	2.3 $\pm$ 0.2	0.06
<b>P; mean <math>\pm</math>SD</b>	1.8 $\pm$ 0.4	1.8 $\pm$ 0.4	1.7 $\pm$ 0.4	0.2
<b>Glucose; mean <math>\pm</math>SD</b>	8.6 $\pm$ 7.5	8 $\pm$ 5	9 $\pm$ 9.2	0.4
<b>BDI; mean <math>\pm</math>SD</b>	7.8 $\pm$ 7.1	9.9 $\pm$ 8.8	5.9 $\pm$ 4.1	0.09 <sup>c</sup>
<b>BDI-FS; mean <math>\pm</math>SD</b>	1.6 $\pm$ 2.4	2.3 $\pm$ 3	1 $\pm$ 1.5	0.04 <sup>c</sup>
<b>BQ; n (%)</b>	56 (56%)	28 (58%)	28 (53%)	0.5
<b>PCS; mean <math>\pm</math>SD</b>	39.8 $\pm$ 10	39 $\pm$ 8	40 $\pm$ 11	0.7 <sup>c</sup>
<b>MCS; mean <math>\pm</math>SD</b>	49 $\pm$ 11	46 $\pm$ 11	53 $\pm$ 9	0.007 <sup>c</sup>

Abbreviations: BDI: Beck Depression Inventory; BDI-FS: Beck Depression Inventory Fast Screening; BMI: body mass index; BQ: Berlin Questionnaire; eGFR: estimated glomerular filtration rate; Hb: hemoglobin; IWG: inter dialytic weight gain; MAP: mean arterial pressure; MCS: Mental Component Summary; PCS: Physical Component Summary; P: phosphate; PP: pulse pressure; PSQI: Pittsburgh Sleep

Quality Index. <sup>a</sup>: Indicates continuity correction; <sup>b</sup>: Indicates likelihood ratio; <sup>c</sup>: Indicates Mann Whitney U test; <sup>d</sup>: Indicates corrected calcium.

In a total of 202 non-dialysis patients, 86 patients were female, and mean age was  $64 \pm 14$ . A total of 70 (35%) patients had an impaired sleep. Female gender, depression, and high risk for sleep apnea were associated with impaired sleep. Lower MCS scores were also correlated with higher risk for poor sleep quality. Patients with an abnormal blood pressure had an increased risk for sleep disturbances according to the results. Table 4.18 shows correlation of sleep quality with various patient characteristics.

**Table 4.17 Baseline characteristics of patients divided by sleep quality in the non-dialysis group**

<b>Variables</b>	<b>Entire cohort</b>	<b>PSQI global score <math>\geq 5</math></b>	<b>PSQI global score <math>&lt; 5</math></b>	<b>P value</b>
<b>N; n (%)</b>	202	70 (35%)	132 (65%)	
<b>Age; mean <math>\pm</math>SD</b>	64 $\pm$ 14	65.5 $\pm$ 14.4	62.8 $\pm$ 14.3	0.2
<b>Gender (female); n (%)</b>	86	41 (59%)	45 (34%)	0.001
<b>BMI (kg/m<sup>2</sup>); mean <math>\pm</math>SD</b>	30 $\pm$ 6	30 $\pm$ 8	29 $\pm$ 5	0.6
<b>Diabetes positive; n (%)</b>	88	32 (46%)	56 (43%)	0.7
<b>Current smokers; n (%)</b>	16	5 (7%)	11 (8%)	0.9 <sup>b</sup>
<b>MAP (mmHg); mean <math>\pm</math>SD</b>	89.7 $\pm$ 10	88.6 $\pm$ 13.2	90.2 $\pm$ 9.5	0.3
<b>PP (mmHg); mean <math>\pm</math>SD</b>	70.4 $\pm$ 20.4	69.5 $\pm$ 24.6	70.4 $\pm$ 17	0.6
<b>Blood pressure</b>				
<b>Normal; n (%)</b>	56 (29%)	18 (27%)	38 (30%)	0.03
<b>High; n (%)</b>	101 (53%)	30 (45%)	71 (57%)	
<b>Low; n (%)</b>	35 (18%)	19 (28%)	16 (13%)	
<b>eGFR ml/min/1.73m<sup>2</sup>; mean <math>\pm</math>SD</b>	36 $\pm$ 16	38 $\pm$ 17	35 $\pm$ 15	0.3
<b>Hb; mean <math>\pm</math>SD</b>	126 $\pm$ 19	125 $\pm$ 20	127 $\pm$ 19	0.4
<b>Albumin; mean <math>\pm</math>SD</b>	35.9 $\pm$ 4.3	36 $\pm$ 4.6	35.9 $\pm$ 4.2	0.9
<b>PTH; mean <math>\pm</math>SD</b>	148 $\pm$ 118	165 $\pm$ 133	141 $\pm$ 111	0.2
<b>Calcium<sup>c</sup>; mean <math>\pm</math>SD</b>	2.11 $\pm$ 0.8	2.4 $\pm$ 1.4	2.4 $\pm$ 1.2	0.17
<b>P; mean <math>\pm</math>SD</b>	1.2 $\pm$ 0.2	1.2 $\pm$ 0.3	1.2 $\pm$ 0.2	0.9
<b>Glucose; mean <math>\pm</math>SD</b>	7.1 $\pm$ 3.2	6.9 $\pm$ 2.9	7.2 $\pm$ 3.4	0.5
<b>BDI; mean <math>\pm</math>SD</b>	3.8 $\pm$ 3.5	5.2 $\pm$ 4.3	3.1 $\pm$ 2.8	0.0001 <sup>a</sup>
<b>BDI-FS; mean <math>\pm</math>SD</b>	0.7 $\pm$ 1.6	1.1 $\pm$ 1.9	0.6 $\pm$ 1.3	0.005
<b>BQ; n (%)</b>	101	43 (61%)	58 (44%)	0.02
<b>PCS; mean <math>\pm</math>SD</b>	43 $\pm$ 10	42.4 $\pm$ 10.8	44.2 $\pm$ 10.6	0.2
<b>MCS; mean <math>\pm</math>SD</b>	55 $\pm$ 7	52.7 $\pm$ 8.1	56.5 $\pm$ 6.8	0.001

Abbreviations: BDI: Beck Depression Inventory; BDI-FS: Beck Depression Inventory Fast Screening; BMI: body mass index; BQ: Berlin Questionnaire; eGFR: estimated glomerular filtration rate; Hb: hemoglobin; MAP: mean arterial pressure; MCS: Mental Component Summary; PCS: Physical Component Summary; P: phosphate; PP: pulse pressure; PSQI: Pittsburgh Sleep Quality Index. <sup>a</sup>: Indicates Mann Whitney U test; <sup>b</sup>: Indicates continuity correction; <sup>c</sup>: Indicates corrected calcium.

## **Chapter 5: DISCUSSION**

### **5.1 Discussion of Results**

This cross-sectional study included a total of 303 CKD patients from the St John's area. The summary of our findings are as follows: (1) MAP, PP, PTH, and P were significantly higher in the dialysis group; (2) PCS and MCS domains of SF-36 were lower in the dialysis group as compared to the non-dialysis group; (3) sleep quality was lower in the dialysis group; (4) depression was more common in the dialysis group; (5) female gender and depression were associated with lower sleep quality; (6) patients with low MCS scores indicated high risk for impaired sleep, sleep apnea, and depression; (7) high PCS and MCS scores were associated with high Hb and eGFR levels; (8) sleep apnea was associated with high BMI and MAP levels; (9) females were 2.5 times more likely to have poor sleep quality; and (10) CNS medication use was associated with impaired sleep.

In the dialysis group, eGFR, Hb, Hct, albumin, and Ca values were significantly lower, whereas PTH and P values were higher as compared to the non-dialysis group. The above differences are as expected for these subgroups. As kidney function declines, P is increased due to reduced renal clearance.<sup>54</sup> As a result of increased P and reduced vitamin D and calcium, a rise in PTH is also expected. Due to malnutrition and chronic inflammation related to uremic toxins and exposure to artificial membranes during hemodialysis, low albumin levels are also expected in the dialysis group.<sup>253,254</sup> Albumin loss through dialysis membranes has also been reported.<sup>254</sup> Erythropoietin secretion is decreased as a result of reduced functioning kidney units, with a subsequent decline in the

number of red blood cells.<sup>255</sup> Due to uremic conditions, the life span of erythrocytes was also reduced.<sup>256</sup> Hb values in the dialysis group would be in part maintained by erythropoietin, which would be less commonly used in the non-dialysis group. Overall, anemia and bone mineral metabolism disturbances are very common problems in dialysis patients.<sup>257</sup>

We found that age was not an independent factor for sleep quality in CKD patients (OR: 1.004, 95% CI: 0.98–1.02, P: 0.59). The correlation between age and sleep quality has been studied in CKD patients, with mixed results. Similar to our findings, age was not a significant factor for sleep quality in dialysis patients, according to a previous report.<sup>205</sup> Monterrosa-Castro et al. studied a total of 1078 middle-aged women for sleep quality and indicated that age was not associated with sleep quality.<sup>258</sup> In contrast, it was reported that age was an important factor for sleep quality in PD patients (r: 0.21, P: 0.01).<sup>259</sup> This was supported in another study that included a total of 212 CAPD patients using the PSQI (r: 0.34, P < 0.001).<sup>177</sup> The mixed results regarding the effects of age on sleep quality might be attributed to the difference in the study populations. We included CKD patients, while other studies included only dialysis patients.

Although age was not associated with poor sleep quality in our report, it was correlated with sleep apnea and depression. Those who were at high risk for sleep apnea and depression were significantly younger than the low-risk group. Similarly, younger patients were more prone to depression in another CKD cohort (P < 0.001).<sup>221</sup> In contrast, other previous reports found higher age to be a predictor for sleep apnea in the

general population.<sup>260</sup> In the general population, as people get older, the risk becomes higher for sleep apnea. In the CKD population, the risk is higher if patients are young.

Our results showed that female gender was associated with a higher likelihood for poor sleep quality (OR: 2.5, 95% CI: 1.5–4.3, P: 0.0001). Parallel to our findings, Huang et al. indicated that female gender was associated with poor sleep (OR: 1.54, 95% CI: 1.23–1.92, P: 0.001).<sup>261</sup> Contrary to these, it was indicated that gender was not associated with sleep quality in dialysis patients.<sup>262</sup> These findings were supported in another report (P: 0.35).<sup>263</sup> Additionally, gender was not associated with sleep quality in children and adolescent CKD patients, according to the report from Davis et al.<sup>264</sup> Different study results in relation to gender and sleep quality are likely due to differences in the study populations. The PSQI was employed for the assessment of sleep problems, excluding the report by Davis and others, which employed the Pediatric Sleep Questionnaire.<sup>264</sup> The reports were all cross-sectional designs.

We found that those who were using a CNS medication had a 3.1-fold increased risk for poor sleep quality (OR: 3.1, 95% CI: 1.8–5.5, P: 0.0001). In a previous report that included 909 incident dialysis patients, benzodiazepine use at the initiation of dialysis was shown to be a significant predictor for poor sleep quality (OR: 0.57, 95% CI: 0.39–0.82).<sup>265</sup> Poor sleep might lead to prescription of hypnotic agents and reverse causality. In another large study, it was shown that CKD patients that sleep less than seven hours per night were more likely to use a sleeping pill as compared to those reporting equal to or more than seven hours of sleep a night (55.7% versus 36.6%, P: 0.002).<sup>266</sup> Additionally, benzodiazepine use was not significantly different between HD patients and healthy age-

and sex-matched controls, according to another report (8.7% versus 4.4%, P: 0.3).<sup>267</sup> A total of 10 (21.7%) patients were reported as benzodiazepine or antidepressant medication users in the same study.<sup>267</sup> Hypnotic or antidepressant treatments were prescribed in 94 (31%) patients in our study group. Overall, study results indicated a high prevalence of benzodiazepine use in kidney patients in response to the patients' sleep-related complaints.

Our study indicated that the mean of some of the scales (PF, RP, and VT) and the PCS summary measure of the SF-36 was lower than the US normative data in the study cohort. Values lower than the general population mean are expected in CKD patients. Additionally, higher scores in the non-dialysis group due to a higher level of kidney function are also expected. Quality of life was previously tested in the CKD population. A total of 30 patients with nephrotic syndrome were studied for quality of life. It was shown that only social functioning was significantly lower than the normative data for the Japanese population.<sup>268</sup> Quality of life was not different between HD and PD patients, according to a previous report.<sup>269</sup>

Quality of life summary scales were also tested for an association with sleep quality. In our study, we found that the MCS domain of SF-36 was correlated with sleep quality, and the most prominent effect was seen when comparisons were made between the highest percentile group and the lower percentiles (OR: 0.3, 95% CI: 0.2–0.6, P: 0.001). We also found that the PCS and MCS scores were negatively correlated with the total PSQI scores (r: -0.16, P: 0.006 for PCS and r: -0.28, P: 0.0001 for MCS). These findings were supported by previous studies. Guney et al. indicated that PCS and MCS scores were

inversely correlated with the global PSQI score (r: -0.41, r: -0.39,  $P < 0.001$  for PCS and MCS scores, respectively).<sup>259</sup> Similarly, it was indicated that PCS and MCS scores were associated with sleep quality (r: -0.45,  $P < 0.001$ , r: -0.41,  $P < 0.001$  for PCS and MCS scores, respectively).<sup>240</sup> Further, impaired sleep quality was shown to be correlated with low PCS and MCS scores in another study.<sup>265</sup> The positive correlation between sleep and life quality indexes is an expected finding due to possible effects of sleep on physical and mental wellbeing. Reverse cause is also possible with those having physical or mental problems finding it harder to sleep undisturbed. Moreover, screening tools for both conditions have some overlap.

We reported that abnormal blood pressure and sleep quality were not related in our logistic models ( $P$ : 0.2 for hypertension and  $P$ : 0.4 for hypotension). However, MAP and PP were significantly higher in the dialysis group, when compared to the non-dialysis group. Further, in our study, we did not find any significant correlation between SBP and DBP with sleep impairment. Similarly, Ji-Rong et al. studied a total of 660 elderly people for the association between hypertension and sleep quality using the PSQI.<sup>270</sup> It was indicated that sleep quality was not associated with hypertension.<sup>270</sup> Hung et al. studied the association between sleep quality and metabolic syndrome, including hypertension using the PSQI in a population-based study.<sup>261</sup> It was reported that hypertension was not correlated with poor sleep quality (OR: 1.03, 95% CI: 0.88–1.21,  $p > 0.05$ ).<sup>261</sup> These findings were also consistent with a previous report by Jennings and others.<sup>271</sup> In contrast, several studies reported that there was an association between non-dipper status, which is defined as blood pressure drop less than 10% during sleep, and sleep quality being tested

with the PSQI, although we did not assess dipping status in our study cohort. Firstly, Yilmaz et al. indicated non-dippers had a higher likelihood of being poor sleepers (OR: 2.95, 95% CI: 1.12–7.74).<sup>272</sup> Erden et al. supported that the non-dipping status and the PSQI global score were associated (OR: 0.84, 95% CI: 0.74–0.94).<sup>93</sup> Huang et al. indicated that non-dippers were more likely to have a poor sleep quality (OR: 2.78, 95% CI: 1.65–6.87).<sup>94</sup> All the aforementioned studies included only hypertensive patients. The correlation between SBP and DBP with the global PSQI scores was reported by Fiorentini (r: 0.55,  $P < 0.001$  for SBP and r: 0.46,  $P < 0.001$  for DBP).<sup>273</sup> The study cohort included a total of 250 patients who were referred for ambulatory blood pressure monitoring, and the prevalence of hypertension was 53%.<sup>273</sup>

Furthermore, Castro et al. studied a total of 1078 middle-aged women in a cross-sectional study for sleep quality using the PSQI.<sup>258</sup> Hypertension was indicated as an independent predictor for poor sleep quality (OR: 0.56, 95% CI: 0.09–1.90,  $P: 0.019$ ).<sup>258</sup> Finally, it was reported that low sleep duration and sleep quality have been associated with an increased risk for hypertension in a review by Palagini and others.<sup>274</sup>

In addition to the adult population, adolescents were studied for the correlation between sleep quality and hypertension.<sup>275</sup> This cross-sectional study involved a total of 3372 students.<sup>275</sup> Values equal to or higher than 135/85 mmHg were considered as indicating hypertension, and sleep quality was assessed using the PSQI.<sup>275</sup> Poor sleep quality was correlated with high BMI measurements and high systolic blood pressure readings.<sup>275</sup> Overall, the predictive value of blood pressure for sleep quality in the non-CKD population has not been well studied, although it was studied with mixed results in the

general population. The data in general support the association, while this study failed to show the same effect, which might be due to limitations about this study. Patients were classified based on one blood pressure measurement and no adjustments took place for presence or absence of blood pressure medications in our study.

Our findings indicated that the presence of diabetes mellitus was not an independent predictor for poor sleep quality (OR: 1.14, 95% CI: 0.72–1.82, P: 0.57). The rate of diabetes did not differ between poor sleepers and good sleepers in our study (48% versus 45%, P: 0.5). The prevalence of diabetes in those with impaired sleep was previously studied. It was reported that diabetes was more common in those with high PSQI global scores (14.9% versus 8.8%,  $P < 0.001$ ).<sup>273</sup>

Further, our results indicated smoking was not related to sleep quality (OR: 1.67, 95% CI: 0.77–3.6, P: 0.19). Contrary to our findings, smoking has been associated with poor sleep quality, according to a previous report (OR: 1.33, 0.75–1.90,  $P < 0.0001$ ).<sup>258</sup> The odds ratio in our study was higher, although it was not significant. The difference might be related to the power of the study, which was affected by the sample size and the proportion of smokers. The sample size in the report by Monterrosa-Castro<sup>258</sup> and others was 1078, whereas it was 303 in our study. Additionally, the confidence interval in our study was wider than the other study, and both confidence intervals were overlapping. As a result, it was not possible to distinguish both studies. Our findings might suggest smoking was correlated with sleep quality, although we did not reach a statistically significant result. Additionally, current smoking status was correlated with sleep quality in a cohort of incident dialysis patients.<sup>265</sup> History of tobacco use was reported as 56.5%

in a HD patient cohort by Unruh et al.<sup>267</sup> We only had a total of 28 (9%) current smokers in the entire cohort. The small number of cases might make it difficult to detect any relation between smoking and sleep quality.

We have demonstrated that BMI was not associated with poor sleep quality (OR: 0.99, 95% CI: 0.96–1.03, P: 0.88) in the study cohort. Similarly, it was reported that the PSQI global score was not correlated with BMI.<sup>272</sup> In contrast, poor sleep quality was shown to be correlated with high BMI in the adolescent population without CKD.<sup>275</sup> The PSQI global score was not correlated with IWG and dialysis vintage in our study (P: 0.7 for IWG and P: 0.8 for dialysis vintage). Previously, Araujo et al. also failed to show a relationship between IWG and sleep quality (P: 0.9).<sup>263</sup>

We reported a significant association between the PCS and MCS scores with hemoglobin in the study cohort (r: 0.32, P: 0.0001 for PCS and r: 0.11, P: 0.05 for MCS). The significance was borderline and about 1% of variance in MCS explained by Hb. The relationship of hemoglobin with SF-36 summary measures was previously examined. It was shown that fatigue and vitality scores were improved after correction of anemia in CKD patients (1.21 versus -2.31, P: 0.036).<sup>239,276</sup> Similarly, it was indicated that the treatment of severe anemia was associated with improved quality of life and reduced transfusion requirements.<sup>277</sup> However, complete correction of anemia has been linked to several adverse health outcomes such as strokes and cardiovascular events (12 versus 4).<sup>239,276</sup> In the same cohort, quality of life scores were later compared between the groups.<sup>239</sup> It was indicated that fatigue scores were improved significantly in the higher target arm (3.2 to 7.9, P: 0.007).<sup>239</sup> Thus, renal anemia management requires careful

consideration of the pros and cons of the treatment, and hemoglobin levels need to be maintained in a narrow therapeutic range.

The present results demonstrate that eGFR as a continuous variable was not a significant determinant for sleep quality in our study cohort, (OR: 0.99 per 1ml/min difference in eGFR, 95% CI: 0.98–1.006, P: 0.28). This finding was supported by a previous report. Roumelioti et al. studied a CKD cohort, which included children and adolescents, to relate eGFR with fatigue and sleeping problems (n: 301).<sup>278</sup> It was indicated that child reported sleeping problems were not significantly different in those with eGFR < 30ml/min/1.73m<sup>2</sup>, when eGFR ≥ 50ml/min/1.73m<sup>2</sup> was the reference category (OR: 0.93, 95% CI: 0.46–1.90).<sup>278</sup> Contrary to these, inadequate sleep has been associated with the severity of kidney dysfunction, according to the report by Plantinga and others.<sup>266</sup> In our study, the association between eGFR and sleep quality was not statistically significant, however 1% change in odds for poor sleep per ml/min change in eGFR may be important.

Our results did not show any significant correlation between the prevalence of sleep apnea and stages of kidney disease (P: 0.3). Similar results were indicated by Plantinga and others, in a large study cohort (n: 9,110).<sup>266</sup> Contrary to these findings, the CKD status was indicated as an independent predictor for sleep apnea, when compared to normal kidney functions (OR: 1.32, 95% CI: 1.13–1.55 for those with eGFR 15–29ml/min/1.73m<sup>2</sup>).<sup>279</sup> The International Classification of Diseases (ICD-9) diagnosis codes for sleep apnea were used to identify the absence or presence of sleep apnea in this study.<sup>279</sup> The ICD-9 diagnosis codes include insomnia or hypersomnia with sleep apnea,

and might include more major cases as compared to diagnosis of sleep apnea using the BQ.

In our study, sleep apnea was not associated with dialysis status (P: 0.37). The gold standard for sleep apnea is a sleep study. Since we employed the BQ for the risk assessment, the relationship might be obscured by false positive or false negative questionnaire results. Further, the applicability of the BQ to CKD patients, especially in dialysis patients might be questionable. Because of the high rates of physical symptoms due to the chronic uremic condition in CKD patients, it is hard to rely on wake-time sleepiness and fatigue to identify sleep apnea. As a result, high false positive rates are expected.

Additionally, female gender and low MCS scores were correlated with poor sleep, as previously indicated by several reports. In regards to kidney damage, we indicated that eGFR was correlated with quality of life index scores. Quality of life was also associated with the degree of anemia. All of these are in support of current knowledge.

Overall, most of our results were consistent with previous reports. We hypothesized that sleeping problems and depression correlate with the degree of kidney dysfunction and hypertension, and these conditions might affect quality of life in CKD patients. eGFR was correlated with depression, but not with sleep quality. We hypothesized that the prevalence of impaired sleep, sleep apnea, and depression would be higher in the group on dialysis than in those with less severe CKD. Poor sleep and depression were more common in the dialysis group, whereas sleep apnea did not differ between groups. We

hypothesized that sleep quality would be correlated with eGFR, blood pressure, and the presence of diabetes, but our data did not support this hypothesis. We hypothesized that impaired sleep quality, sleep apnea, and depression would be associated with poorer quality of life, and this was supported by our data.

Some findings were different from others, and probably due to the differences in the study populations, assessment methods, and by chance alone. We did not show a significant correlation between blood pressure parameters (SBP, DBP, MAP, and PP) and sleep quality. Several previous reports using ambulatory blood pressure monitoring indicated that blood pressure and dipping status were associated with impaired sleep.<sup>272,93,94</sup> We measured blood pressure on one occasion, which might make it difficult to identify any possible correlation between sleep and blood pressure. Moreover, sleep apnea was not associated with degree of kidney dysfunction. This finding is not consistent with a previous report,<sup>279</sup> and a lack of an actual sleep study for sleep apnea diagnosis in our study might be the reason.

## **5.2 Strengths of the Study**

This study has several strengths that need to be noted. Firstly, the sample size was large enough to accommodate patients with various levels of kidney dysfunction. As a result, comparisons were made between different stages of CKD. Furthermore, blood pressure was measured using an automated device, which reduced the risk for measurement bias. Additionally, race may be a confounder in various patient outcomes. This present report

is not biased by an effect of race since a total of 99% of the study cohort was Caucasian; therefore, the results might be applied to other Caucasian populations with CKD.

Other strengths of the study include methods related to administration and scoring of the instruments. All interviews were performed by the principal investigator, which reduced the chance of interobserver errors. However, there was still a risk for measurement bias, especially when leading the participant to answer the questions. Further, all questionnaires were administered on one occasion, and scored by the same person who was blinded to the level of kidney dysfunction, excluding the dialysis group at the time of the interview. As a result, interobserver errors were eliminated completely, although other potential biases such as observer-expectancy effect might have occurred due to involvement of the principal investigator in the interview process. Additionally, SF-36 questionnaire was scored by the software which decreases the likelihood for incorrect calculation.

### **5.3 Limitations of the Study**

There are several limitations to this study. The common drawbacks of cross-sectional studies also apply to the present report. First of all, since it is a cross-sectional study, inference of causality is not possible. Therefore, we only tested associations of sleep problems and depression. Further, the study would be more prone to biases, such as selection bias due to convenience sampling and information bias, because of reduced control over external sources. Since we collected most of our data from questionnaires,

this study was prone to information bias. For example, social desirability might affect the respondents' answers to some questions.

Additionally, we had only seven cases on PD treatment, although the study included a large number of patients. Therefore, it was not possible to assess the difference between dialysis modalities. We also had 18 patients with a kidney transplant, limiting inferences for this subgroup. Moreover, some analyses yielded wide confidence intervals suggesting precision of these estimates might lack power.

One of the settings for the questionnaire administration was in the outpatient clinics, and some patients did not agree to participate as they would have needed to spend extra time to answer the questionnaires. This might have posed a risk for a respondent bias. Completeness of data for all variables varied, as previously discussed. Moreover, the potential for data to be missing from the charts regarding medication use might lead to misclassification, and was another weakness of the study.

Alcohol utilization, opiate use, and comorbidities such as malignancy, peripheral artery disease, and coronary artery disease were also not included in this study. Accuracy was one of our biggest concerns. The information related to comorbidities was not reliable. The medical record would need to explicitly indicate the presence or absence of each comorbidity of interest to make the analyses reliable, and that was not the case in this retrospective part of the dataset. We were only able to verify accuracy of information related to diabetes mellitus. Information related to albuminuria, as well as opiate and alcohol use was not consistently available either. As a result, we decided to only focus on

certain parameters when we designed the study and wrote the protocol. Thus, some relevant information had to be left due to unavailability and/or inaccessibility of the data.

Another limitation was the absence of a sleep study and structured clinical interview, which are the gold standards for diagnosis of sleep quality and depression, respectively. Thus, having a strong conclusion is not permitted without a higher degree of certainty about the diagnosis. Further, blood pressure measurement was arbitrary as a single value might not represent the full spectrum of possible fluctuations.

There were also several problems with the questionnaires. Firstly, most of the patients, especially those on dialysis treatment, exhibited diminished aptitude for reading. As a result of reduced attention and concentration functions, reading comprehension can be suppressed in kidney patients. Thus, the applicability of questionnaire-based studies can be restricted in kidney patients as a result of a lack of interest in completing pen-and-paper responses. In such cases, an interview was employed to collect data. During the interviews, socially acceptable answers might have been given rather than completely truthful answers and thus there was an increase in the likelihood of information bias.

Furthermore, patients preferred to skip several questions in the BDI. There was not a regular pattern in the skipped questions, which may have led to a systematic bias. All unanswered questions were considered as equivalent to an answer of no. As a result, we had very few positive depression cases (9% in the study cohort using the BDI-FS), and we reported low depression rate. This may not be an accurate reflection of the reality, and we might miss some positive cases for depression. However, our prevalence was

consistent with a previous report in CKD patients by Feng and others (n: 364, prevalence of depression: 13%).<sup>280</sup> Further, a general health-related quality of life scale was administered in this study. Since disease-specific domains were not included, some important information may be missing related to specific effects of kidney disease on daily life.

#### **5.4 Implications for Practice**

The prevalence of sleep problems and depression are higher in kidney patients as compared to the normal population.<sup>197,221</sup> These conditions have been related to lower quality of life and survival rates both in the general population and CKD patients.<sup>199-202,221</sup>

Our results indicated a high burden of sleep disturbances in kidney patients, while depression prevalence was 9% using BDI-FS as a screening tool. Kidney dysfunction, particularly the need for dialysis, was related to quality of life and depression. Since life expectancy is already significantly reduced in CKD patients, all appropriate measures to improve longevity and quality of life should be considered in the management of these patients.

In our experience, the PSQI was easy to use to evaluate sleep quality. Due to the high burden of sleeping disturbances in kidney patients, it can be an acceptable instrument in clinical practice for those with sleeping problems. Since our results indicated that the dialysis population had higher global PSQI scores than the non-dialysis group, detailed and diligent history-taking for sleep-related issues are required in the dialysis patients.

In addition to sleep evaluation, it was suggested that the PSQI could be used as a screening tool for cardiovascular risk assessment in the general population.<sup>273</sup> However,

there is not sufficient evidence to support a direct correlation between the global PSQI scores and patient outcomes. The associations are even less clear in kidney patients.<sup>205</sup> As a result, the application of the PSQI as a screening tool to predict cardiovascular risk and/or sleep quality might be labour intensive, futile, and cumbersome as a routine practice.

Further, one of the most common causes of poor sleep is sleep apnea, and it is prevalent in CKD patients.<sup>197</sup> A high-prevalence rate of sleep apnea was also consistent with our findings, but the causality may not be inferred as this was a cross-sectional study. Sleep apnea has been associated with adverse short-term consequences, such as accidents, and long-term consequences, such as cardiovascular events.<sup>92,107,281</sup> As cardiovascular event rates are already high in CKD patients, a comprehensive approach to reducing the risk should be employed. Evidence suggests that CPAP treatment for sleep apnea reduces cardiovascular events and mortality.<sup>282</sup> Similarly it was indicated that CPAP was associated with improved longevity and quality of life in kidney patients.<sup>283</sup> However, cost and patient acceptance may reduce the uptake of CPAP therapy. Moreover, sleep apnea has been associated with depression in our study. A detailed history should be taken in all depressive CKD patients to diagnose sleep apnea, as it might be a correctable underlying contributor to depression.<sup>283</sup>

Although it is important to recognize and manage sleep apnea due to its link to depression and increased rates of cardiovascular incidents, diagnosis of sleep apnea might be challenging because of atypical presentation and a lack of highly validated tools for screening purposes in kidney patients.<sup>43</sup> The BQ is a validated tool for sleep apnea in the general population.<sup>17</sup> Nevertheless, the instrument might be associated with frequent false

positive responses in dialysis patients due to the second component of the questionnaire, which measures wake-time sleepiness and fatigue. The second component is considered positive in those with fatigue after sleep at least three or four times per week. This is a common finding, especially in HD patients probably due to the intermittent nature of the treatment and the associated rapid changes in the blood parameters.<sup>284,285</sup>

Depression is a mental state of feeling guilty, punished, and like a failure, and is associated with an exacerbating self-criticism.<sup>136</sup> People might seem very friendly and nice to others even when they are severely depressed. Physicians who only rely on their clinical judgment without the standard clinical interview or a screening tool for depression might underdiagnose the condition, which may be life-threatening in the case of suicide.<sup>251</sup> Given the high prevalence in CKD patients, it is important to assess patients at least semi-annually as recommended by the KDOQI guidelines.<sup>64</sup> Recognition and management of the condition may improve patient satisfaction and quality of life, although safety and effectiveness of antidepressant treatment in CKD patients is controversial.<sup>232</sup> In our experience, we recognize the BDI-FS as a brief and easily administered method for depression screening as it only questions the mental state of the patients. The BDI has questions related to both physical and mental components. As a result, the BDI is more time-consuming and might be misleading due to the effects of the uremia on general physical wellbeing.

Lastly, defense mechanisms are unconscious coping systems that work to reduce the level of anxiety for an unacceptable impulse.<sup>286</sup> Denial is one of the defense mechanisms that might lead to reality distortion by ignoring the problem.<sup>286</sup> Patients who have chronic health conditions might use the denial defense mechanism when they are incapable of

accepting the problem.<sup>287</sup> When a question is posed regarding their physical and mental capability, the defense mechanism is destroyed as the unconscious state is cancelled out. As a result, the patient may recognize and accept the problem at that point. If the direction of the treatment is not expected to be changed according to the results of the questionnaire, it might not be beneficial to apply the tool, especially to those patients with irreversible conditions.

To conclude, the PSQI might be employed in those with sleep disturbances, especially in dialysis patients. The BDI-FS is a practical and valid tool to evaluate depression, and can be used in kidney patients annually or semi-annually. The BQ is validated for sleep apnea screening in the general population;<sup>17</sup> however, it might not be a reliable instrument in dialysis patients. One of the components of the BQ assesses day-time functioning, which can be affected by uremic toxins.<sup>284,285</sup> SF-36 is a valid tool, but the results do not affect the practice pattern in CKD patients most of the time. Thus, it needs to be employed in selected cases with careful consideration of its possible negative emotional impact on patients.

Overall, screening for depression and evaluation of sleep disorders in symptomatic cases are important in CKD patients. Although the effectiveness and safety of antidepressant treatment is not clear in kidney patients, antidepressant therapy, anxiolytic therapy, and hospitalization are needed if the patient has suicidal or homicidal thoughts and severe depression.<sup>232</sup> Sleep apnea might be treated efficiently with CPAP.<sup>132,133</sup> Additionally, providing adequate dialysis for solute and fluid removal, and maintaining guideline-appropriate targets might also be important in the management of sleep problems,

including sleep apnea, as well.<sup>288</sup> Both conditions have been correlated with negative patient-oriented outcomes.<sup>13,113,114,140</sup>

## **5.5 Implications for Research**

Normal functioning of the hypothalamo-pituitary-adrenal axis is required for resolving sleep problems and depression.<sup>117,118,148</sup> Additionally, the normal state may also improve or protect the current kidney functions.<sup>289</sup> Although the components and interactions of the system are extensively studied, there are still poorly understood aspects that deserve further investigation.

Sleep is a valuable avenue to explore and understand the complex function and structure of the autonomic nervous system and its interaction with the HPA axis. The tools to reestablish sympathico-vagal balance are not fully successful at present; however, newly emerging techniques to control overactive sympathetic tone are promising, such as radiofrequency ablation of renal sympathetic nerves.<sup>290,291</sup> Further research is needed to increase knowledge and experience and to solidify the benefits of the techniques. Abnormalities in the functioning of the autonomic nervous system might underlie sleep problems, especially sleep apnea and depression.<sup>117,118,142,143</sup> Novel approaches to resetting these systems might be helpful in controlling sleep and mood disorders.

Exploring the complexity of the relations between poor sleep, sleep apnea, depression, and kidney dysfunction requires large-scale studies that employ accepted gold-standard tests for diagnosis of the conditions. The association between the components of the metabolic syndrome, sleep disturbances, and depression might also accommodate more

research in the field. In particular, stronger designs to assess the causality of the observed associations are required to inform not only current therapies, but also research into even more effective therapies in the future. Although clinical presentations may differ substantially, the underlying causal pathophysiological pathways for sleep disturbances, depression, and overactive renin angiotensin aldosterone system, which is a major threat for kidney function loss, may share common features linked to the autonomic nervous system and the HPA axis.<sup>117,118</sup> Therefore, these factors need to be elucidated in future research.<sup>117,118,142,143</sup>

## **Chapter 6: CONCLUSION**

This study tested factors related to sleep quality, depression, and quality of life in CKD patients. Sleep quality was not correlated with eGFR, blood pressure, and presence of diabetes. Poor sleep quality, sleep apnea, and depression were associated with lower quality of life scores. CNS medication use was more common in the dialysis group and associated with poor sleep quality. Gender, marital status, risk for sleep apnea, depression, and MCS scores were correlated with sleep quality. Age, BMI, MAP, depression, and PCS and MCS scores were associated with the risk for sleep apnea. Age, gender, and kidney dysfunction were correlated with depression in our study. Hemoglobin and eGFR were correlated with both quality of life summary measures. The prevalence of impaired sleep and depression were higher in the group on dialysis than in those with less severe CKD. A total of 117 (39%) patients were poor sleepers, while the prevalence of depression was 9.4% using BDI-FS. Stage of CKD was not correlated with sleep quality, but was with depression. Female gender and either an antidepressant use or a hypnotic treatment doubled or tripled the risk for poor sleep quality, according to our results. In the non-dialysis group, female gender, being depressed, and low MCS scores were related to impaired sleep. In the dialysis patients, on the other hand, a high risk for sleep apnea appeared to be tied significantly with sleep quality in addition to female gender, depression, and low MCS scores.

The high prevalence rates of sleep problems and low quality of life scores were similar to the findings of others. The findings suggest a need for more robust studies that assess the causality of these associations, as well as further work on underlying pathophysiological

mechanisms. In the meantime, large-scale studies in CKD patients for predictors of poor sleep quality and depression might be recommended. Prospective cohort studies would be a reasonable choice to shed considerable light on predictors of both conditions. Polysomnography and the structured clinical interview need to be employed to more firmly establish the diagnosis of sleep apnea and depression, respectively. In the meantime, BDI-FS may be employed in nephrology practice, since depression screening is a vital component of the standard care of CKD patients. The PSQI may also be used for sleep quality evaluation in symptomatic patients.

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## **APPENDICES**

### **Appendix A: Data Abstraction Form**

ID number:

Age:

Race:

Gender:

Marital status

Height:

Weight

Smoking:

Current (Y/N)

Past or never (Y/N)

Diabetes mellitus(Y/N):

Dialysis vintage:

Vascular access

eGFR by the MDRD formula

PTH

Ca

P

Albumin

Hematocrit

Hemoglobin

Current medications:

Sedatives

Antidepressant

Blood pressure

Inter-dialytic weight gain

Dialysis modality

The scores form the questionnaires:

The Beck Depression Inventory

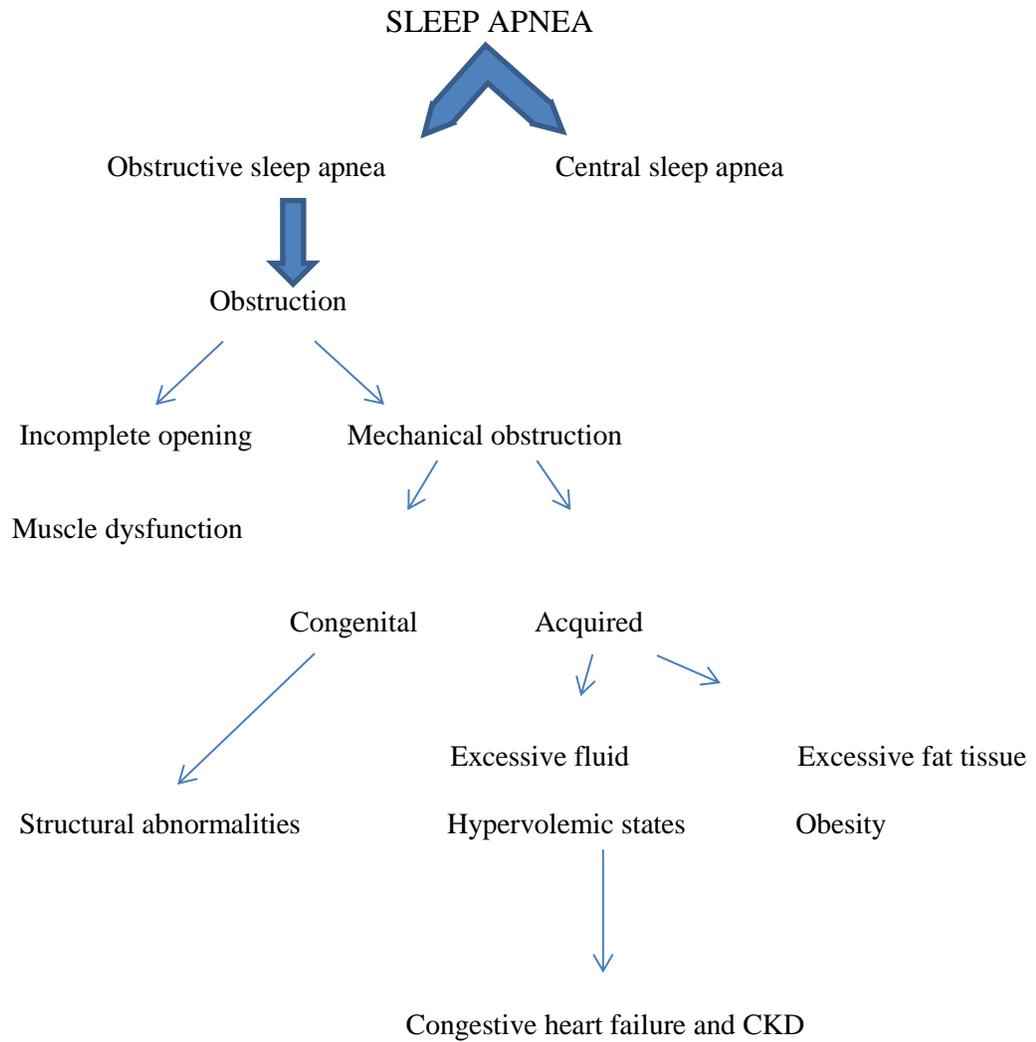
The Beck Depression Inventory Short form

The Berlin Questionnaire

The Pittsburgh Sleep Quality Index

The SF-36

## Appendix B: Mechanisms for Sleep Apnea



## Appendix C: Flowchart for Pathogenesis of Depression

Reduced Glutamic acid decarboxylase (GAD) 65 and 67



Reduced Gamma Amino Butyric acid (GABA)



Increased Corticotrophin Releasing Hormone (CRH)

[Overactive hypothalamic-pituitary-adrenal axis]



Increased adrenocorticotrophic hormone (ACTH)

Adrenal cortex

Adrenal medulla



Glucocorticoids increased

NE and E increased:<sup>292</sup>

Increased blood flow in adrenals

Increased direct secretion of NE and E

Increased tyrosine hydroxylase and dopamine beta- hydroxylase

## Appendix D: Diagram for Normal Sleep

