PART 6. ASSOCIATION OF LEVEL OF GFR WITH COMPLICATIONS IN ADULTS

MANY OF THE complications of chronic kidney disease can be prevented or delayed by early detection and treatment. The goal of Part 6 is to review the association of the level of GFR with complications of chronic kidney disease to determine the stage of chronic kidney disease when complications appear. As described in Appendix 1, Table 153, the Work Group searched for cross-sectional studies that related manifestations of complications and the level of kidney function. Data from NHANES III were also analyzed, as described in Appendix 2.

Because of different manifestations of complications of chronic kidney disease in children, especially in growth and development, the Work Group limited the scope of the review of evidence to adults. A separate Work Group will need to address this issue in children.

The Work Group did not attempt to review the evidence on the evaluation and management of complications of chronic kidney disease. This is the subject of past and forthcoming clinical practice guidelines by the National Kidney Foundation and other groups, which are referenced in the text.

Representative findings are shown by stage of chronic kidney disease in Figs 15 and 16. Figure 15 shows a higher prevalence of each complication at lower GFR. Figure 16 shows a larger mean number of complications per person and higher prevalence of multiple complications at lower GFR. These and other findings support the classification of stages of chronic kidney disease and are discussed in detail in Guidelines 7 through 12.

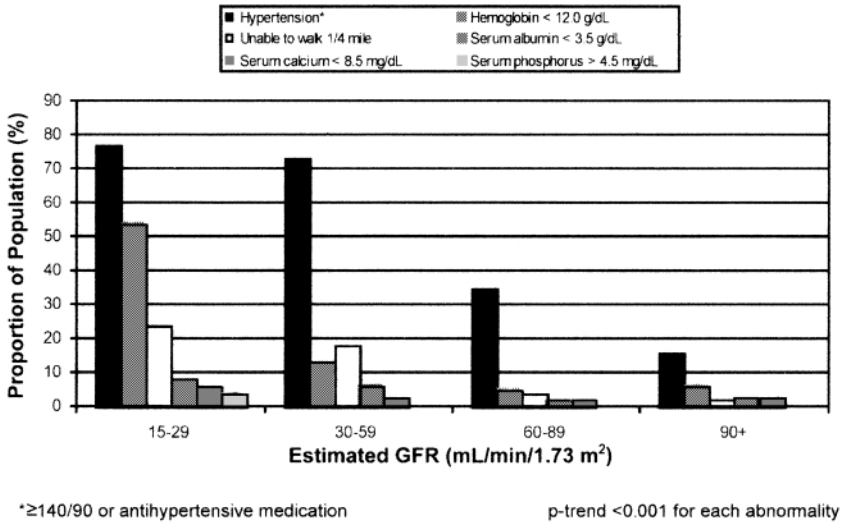

Fig 15. Estimated prevalence of selected complications, by category of estimated GFR, among participants age ≥20 years in NHANES III, 1988 to 1994. These estimates are not adjusted for age, the mean of which is 33 years higher at an estimated GFR of 15 to 29 mL/min/1.73 m^2 than at an estimated GFR of ≥90 mL/min/1.73 m^2.

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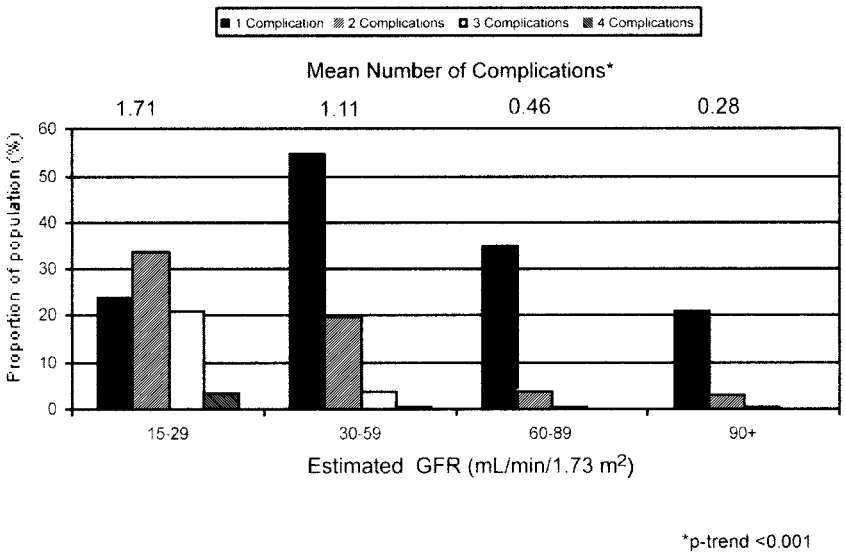

Fig 16. Estimated distribution of the number of complications, by category of estimated GFR among participants age ≥20 years in NHANES III, 1988 to 1994. These estimates are not adjusted for age, the mean of which is 33 years higher at an estimated GFR of 15 to 29 mL/min/1.73 m^2 than at an estimated GFR of ≥90 mL/min/1.73 m^2.

GUIDELINE 7. ASSOCIATION OF LEVEL OF GFR WITH HYPERTENSION

High blood pressure is both a cause and a complication of chronic kidney disease. As a complication, high blood pressure may develop early during the course of chronic kidney disease and is associated with adverse outcomes—in particular, faster loss of kidney function and development of cardiovascular disease.

- **Blood pressure should be closely monitored in all patients with chronic kidney disease.**
- **Treatment of high blood pressure in chronic kidney disease should include specification of target blood pressure levels, nonpharmacologic therapy, and specific antihypertensive agents for the prevention of progression of kidney disease (Guideline 13) and development of cardiovascular disease (Guideline 15).**

BACKGROUND

High blood pressure can be either a cause or a consequence of chronic kidney disease. Adverse outcomes of high blood pressure in chronic kidney disease include faster decline in kidney function and cardiovascular disease. The appropriate evaluation and management of high blood pressure remains a major component of the care of patients with chronic kidney disease.

High blood pressure is a well-recognized public health problem in the United States. Based on epidemiological data from the National High Blood Pressure Education Program and the National Health and Nutrition Examination Surveys, the rates of detection, treatment, and control of high blood pressure have improved dramatically over the past five decades. Concomitantly, the rates of stroke, myocardial infarction, and heart failure have decreased by approximately 15% to 40%.[244] However, during the same time, high blood pressure as a cause of ESRD has increased at an annualized rate of 10% for the last several years, and cardiovascular disease is the leading cause of death in ESRD.[4,245,246] In part this may be due to inadequate control of high blood pressure in patients with chronic kidney disease.

In 1998, the NKF published the Report of the Task Force on Cardiovascular Disease in Chronic Renal Disease.[9] One of the major goals of the Task Force was to assess current knowledge about the association of high blood pressure and cardiovascular disease in chronic kidney disease. Portions of the Task Force Report are reproduced

in this guideline with permission of the authors.[247,248] More recently, the NKF published a Report on Management of Hypertension in Adults with Renal Diseases and Diabetes from the Executive Committees of the Councils on Hypertension and Diabetic Kidney Disease.[249]

In July of 2001, the NKF initiated a K/DOQI Work Group specifically to conduct a detailed review of evidence and to develop clinical practice guidelines for the management of blood pressure in chronic kidney disease to prevent progression of kidney disease and development and progression of cardiovascular disease in chronic kidney disease. The goal of this guideline is to provide a selected review of the literature relating high blood pressure to adverse outcomes of chronic kidney disease and to describe the association of the level of GFR with high blood pressure, as reported in NHANES III. Guideline 13 describes the relationship of high blood pressure to progression of kidney disease.

RATIONALE

Definition

Consensus panels in the United States and other countries have defined hypertension in adults as systolic blood pressure greater than 140 mm Hg and/or diastolic blood pressure greater than 90 mm Hg. The Sixth Report of the Joint National Committee for the Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC-VI) classifies categories of blood pressure levels as shown in Table 71.

Table 71. Classification of Blood Pressure for Adults Age ≥18 Years (JNC-VI)

Category	Systolic Blood Pressure (mm Hg)		Diastolic Blood Pressure (mm Hg)
Optimal	<120	*and*	<80
Normal	<130	*and*	<85
High-Normal	130–139	*or*	85–89
High	≥140	*or*	≥90
Stage 1	140–159	*or*	90–99
Stage 2	160–179	*or*	100–109
Stage 3	≥180	*or*	≥110

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Table 72. Pathogenetic Mechanisms of High Blood Pressure in Chronic Kidney Disease

Pre-existing essential hypertension
Extracellular fluid volume expansion
Renin-angiotensin aldosterone system stimulation
Increased sympathetic activity
Endogenous digitalis-like factors
Prostaglandins/bradykinins
Alteration in endothelium-derived factors (nitric oxide/endothelin)
Increased body weight
Erythropoietin administration
Parathyroid hormone secretion/increased intracellular calcium/hypercalcemia
Calcified arterial tree
Renal vascular disease and renal arterial stenosis
Chronic allograft dysfunction
Cadaver allografts, especially from a donor with a family history of hypertension
Cyclosporine, tacrolimus, other immunosuppressive and corticosteroid therapy

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JNC-VI recommends a goal blood pressure of <140/90 mm Hg for individuals with high blood pressure without diabetes, cardiovascular disease, or chronic kidney disease. For individuals with high blood pressure and decreased kidney function, the recommended goal is <130/85 mm Hg.

Strength of Evidence

High blood pressure develops during the course of chronic kidney disease (R). High blood pressure is a well-described complication of chronic kidney disease. The prevalence of high blood pressure is approximately 80% in hemodialysis patients and 50% in peritoneal dialysis patients.[250,251] In patients with earlier stages of kidney disease, high blood pressure is also highly prevalent, varying with patient characteristics such as the cause of kidney disease and level of kidney function.[252] There are many causes of high blood pressure in chronic kidney disease. The clinically more important pathogenetic mechanisms of high blood pressure are listed in Table 72.[248]

High blood pressure is associated with worse outcomes in chronic kidney disease (R). In the general population, there is a strong, graded relationship between the level of blood pressure and all-cause mortality and fatal and nonfatal cardiovascular disease. Optimal levels of sys-

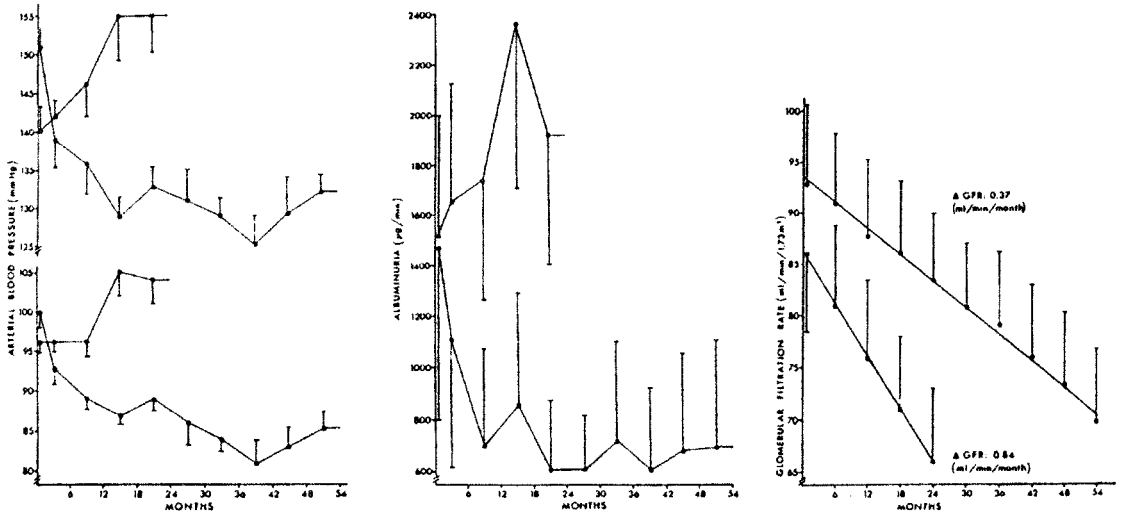


Fig 17. Relationship between blood pressure and progression of diabetic kidney disease. Mean arterial blood pressure, albumin excretion rate, and GFR in patients with type 1 diabetes randomly assigned to a reduction in mean arterial pressure of 10 mm Hg using metoprolol at 100 to 400 mg/d, hydralazine at 50 to 200 mg/d, and furosemide at 80 to 500 mg/d versus no antihypertensive therapy. Solid circles represent the treated group. Open circles represent the control group. Vertical lines represent standard error. Study was stopped earlier in the control group because of faster decline in GFR. Reprinted with permission.[253]

tolic and diastolic blood pressure are defined as less than 120 and 80 mm Hg, respectively. Among patients with chronic kidney disease, there is also substantial evidence of a relationship between elevated levels of blood pressure and cardiovascular risk. In addition, high blood pressure is associated with a greater rate of decline in kidney function and risk of development of kidney failure. However, the optimal level of blood pressure to minimize adverse outcomes for cardiovascular and kidney disease has not been established.

Progression of kidney disease. This subject is reviewed in more detail in Guideline 13. The following represent a few of the many studies that demonstrate these relationships.

Diabetic kidney disease. Numerous epidemiological studies and clinical trials have shown a relationship between the level of blood pressure and faster progression of diabetic kidney disease. Figure 17 shows the relationship in one of the earliest randomized trials.[253]

Nondiabetic kidney diseases. The Modification of Diet in Renal Disease Study showed a significant relationship between the rate of decline in GFR and level of blood pressure among patients with predominantly nondiabetic kidney disease. This relationship was affected by the baseline level of urine protein (Fig 18).[255]

Diseases in the kidney transplant. A relationship between level of blood pressure and progression of kidney disease has now been shown among kidney transplant recipients. The Collaborative Transplant Group documented that higher

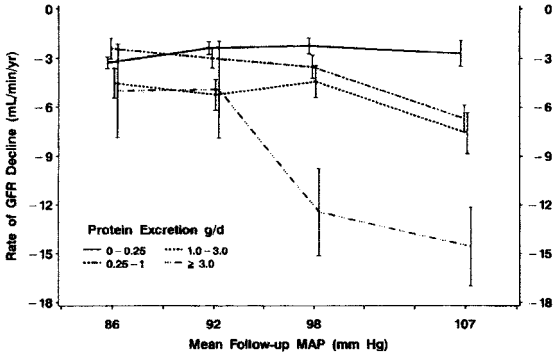


Fig 18. Relationship between mean arterial blood pressure and GFR decline. Mean GFR decline and achieved follow-up blood pressure in MDRD Study A (patients with baseline GFR 25 to 55 mL/min/1.73 m²). Regression lines relating the estimated mean GFR decline over 3 years to mean follow-up MAP for groups of patients defined according to baseline proteinuria. Within each group, a 3-slope model was used with break points at 92 and 98 mm Hg. Reprinted with permission.[255]

blood pressure after kidney transplantation is associated with more rapid development of graft failure[256] (Fig 19).

Cardiovascular disease and mortality. The prevalence of cardiovascular disease and related outcomes in patients with decreased GFR has not been evaluated in large-scale epidemiological studies, and little is known about CVD mortality and morbidity in these patients. Several studies have shown a high prevalence of left ventricular hypertrophy (LVH) in patients with decreased GFR and patients beginning dialysis. In one study, a higher level of systolic blood pressure, lower level of kidney function, more severe anemia, and older age were independently associated with higher left ventricular mass index.[257] A few studies have shown a relationship between higher systolic blood pressure and clinical cardiovascular disease events.[258,259] Among dialysis patients, higher blood pressure is clearly associated with development of cardiovascular disease. Table 73 shows the relationship between mean arterial pressure and various cardiovascular disease outcomes in a prospective cohort of incident dialysis patients.[260] Left ventricular hypertrophy and congestive heart failure were both strongly associated with subsequent mortality. However, lower rather than higher blood pressure was associated with a higher risk of death.

The association between level of blood pressure and mortality does not appear to be consistent, with a number of studies reporting either positive or negative associations.[248] One recent study showed a bimodal distribution ("U-shaped" relationship) with excess risk in hemodialysis patients with normal or low blood pressure, as well as in patients with very high blood pressure[262] (Fig 20). It is likely that excess risk in patients with low blood pressure reflects confounding effects of underlying or pre-existing cardiovascular disease on mortality, while the true relationship of blood pressure to mortality is reflected in the excess risk in patients with very high blood pressure as in the general population.

Overall, these studies demonstrate that high blood pressure is associated with faster progression of chronic kidney disease, development of cardiovascular disease, and, likely, higher mortality in patients with chronic kidney disease.

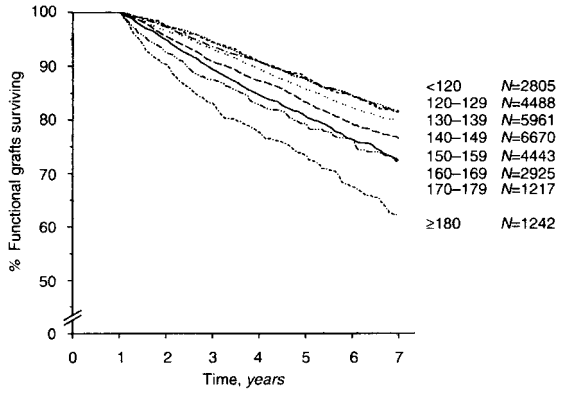


Fig 19. Relationship between systolic blood pressure and graft survival. Association of systolic blood pressure at 1 year with subsequent graft survival in recipients of cadaveric kidney transplants. Ranges of systolic blood pressure value in mm Hg and number of patients studied in the subgroups are indicated. The association of systolic blood pressure with graft survival at seven years was statistically significant ($P < 0.0001$). Reproduced with permission.[256]

Table 73. Association of Mean Arterial Pressure and Cardiovascular Disease Events in Incident Dialysis Patients

Outcome	Relative Risk*	P-value
Normal LV (reference)	—	—
Concentric LVH	1.48	0.02
LV dilatation	1.48	0.06
Systolic dysfunction	—	NS
Ischemia	1.39	0.05
CHF	1.44	0.007
Death	0.82	0.009

* Relative risks are for 10 mm Hg higher mean follow-up monthly mean arterial pressure before the index event, controlling for age, diagnosis of diabetes, ischemic heart disease at onset of ESRD, follow-up monthly mean serum albumin and hematocrit. Data from Foley et al.[261] Reprinted with permission.[248]

Abbreviations: CVD, cardiovascular disease; LV, left ventricle; LVH, left ventricular hypertrophy; CHF, congestive heart failure; NS, not significant

Prevalence of high blood pressure is related to the level of GFR. Patients with chronic kidney disease have a high prevalence of high blood pressure, even when GFR is only mildly reduced (S). Figure 21 shows the relationship between GFR and prevalence of hypertension among 1,795 patients in the baseline cohort of the MDRD Study.[263] At GFR levels of 60 to 90 mL/min/

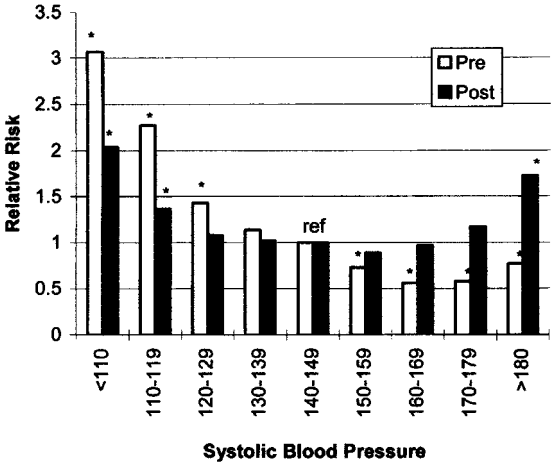


Fig 20. Mortality versus systolic blood pressure in hemodialysis patients. Dialysis Clinic, Inc. prevalent cohort (1992 to 1996, n = 5433).[262] Cox regression analysis including age, race, gender, and diagnosis as baseline covariates, and predialysis or postdialysis systolic blood pressure, albumin, and Kt/V as time-dependent covariates. Reprinted with permission.[248]

1.73 m^2, the prevalence of high blood pressure was approximately 65% to 75%. In this study, high blood pressure was defined by patient history (including the use of antihypertensive medications) and medical records, rather than the level of blood pressure. In addition to GFR level, the prevalence of high blood pressure was significantly greater among men and individuals with higher body mass index, black race, and older age.

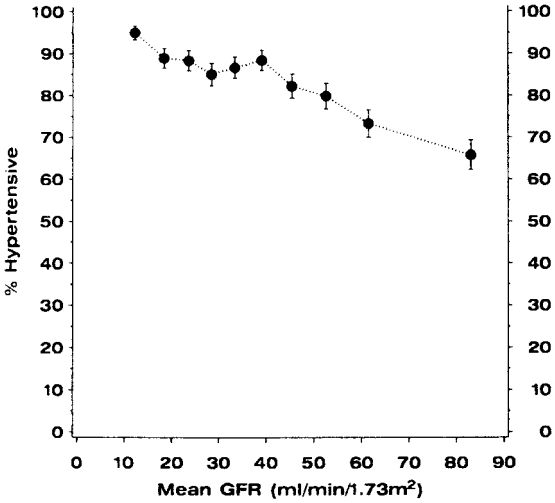


Fig 21. Prevalence of high blood pressure by level of GFR in the MDRD Study. High blood pressure was defined as classification by study investigators based on patient history (including the use of antihypertensive drugs) and review of medical records. GFR was measured by urinary clearance of ^{125}I-iothalamate. Patients were ranked by GFR into 10 groups, each containing 179 or 180 patients. Data are presented as mean values ± standard errors.

Figure 22 shows the prevalence of high blood pressure by level of GFR among 15,600 patients participating in the NHANES III. Two levels of high blood pressure are depicted: JNC Stage 1 or greater (systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg, or taking medications for high blood pressure); and JNC Stage 2 or greater (systolic blood pressure ≥160 mm Hg or diastolic blood pressure ≥100 mm Hg).

In NHANES III, the approximately 40% prevalence of high blood pressure among individuals with GFR of approximately 90 mL/min/1.73 m^2 was lower than in the MDRD Study, presumably because not all patients with GFR in this range in NHANES III had chronic kidney disease. Among patients with lower GFR, the prevalence of high blood pressure is similar to that observed in the MDRD Study. Notably, the prevalence of JNC Stage ≥2 high blood pressure is approximately 20% among individuals with GFR 15 to 30 mL/min/1.73 m^2, which is approximately 2-fold greater than among patients with higher GFR.

High blood pressure is not optimally controlled in patients with chronic kidney disease (S). A recent analysis of the NHANES III database assesses the level of blood pressure control among individuals with decreased kidney func-

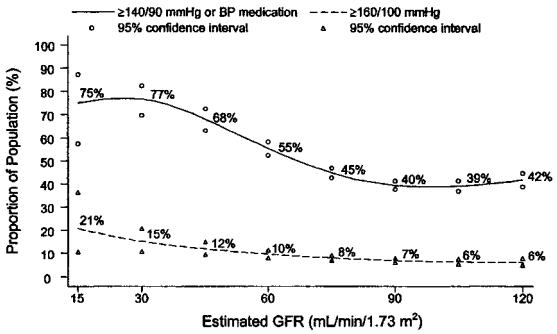


Fig 22. Prevalence of high blood pressure by level of GFR, adjusted to age 60 years (NHANES III). Predicted prevalence of high blood pressure among adult participants age 20 years and older in NHANES III, 1988 to 1994. Values are adjusted to age 60 years using a polynomial regression. 95% confidence intervals are shown at selected levels of estimated GFR.

tion.[5] Decreased kidney function was defined as elevated serum creatinine (≥1.6 mg/dL in men or ≥1.4 mg/dL in women).

An estimated 3% (5.6 million) of the US population had elevated serum creatinine according to this definition, and of these 70% had high blood pressure. Among individuals with decreased kidney function and high blood pressure, 75% received treatment. However, only 11% of individuals with high blood pressure and elevated serum creatinine had blood pressure <130/85 mm Hg, and 27% had blood pressure <140/90. Treated individuals had a mean blood pressure of 147/77 mm Hg, with 48% prescribed only one antihypertensive medication. Thus, it appears that additional efforts will be necessary to lower systolic blood pressure. Multi-drug therapy may be necessary in the majority of patients.

Figures 23 and 24 show the prevalence and number of individuals with elevated serum creatinine among patients receiving and not receiving antihypertensive therapy, according to blood pressure category. The largest number of treated and untreated individuals have JNC Stage 1 high blood pressure (140 to 159/90 to 99 mm Hg).

Treatment of high blood pressure in chronic kidney disease should include specification of target blood pressure levels, nonpharmacologic therapy, and specific antihypertensive agents for the prevention of progression of kidney disease (Guideline 13) and development of cardiovascular disease in patients with chronic kidney disease (Guideline 15) (R). Specific recommendations for evaluation and management of high blood pressure in chronic kidney disease are beyond the scope of this guideline. The investigation of antihypertensive agents to prevent or delay the progression of chronic kidney disease and development of cardiovascular disease is a rapidly evolving. A number of guidelines and recommendations have been developed. In addition, the role of non-pharmacologic therapy for the treatment of high blood pressure, and as adjuncts in the prevention and treatment of cardiovascular disease, are also under investigation. Recommendations by other groups and recent studies are reviewed in Guidelines 13 and 15.

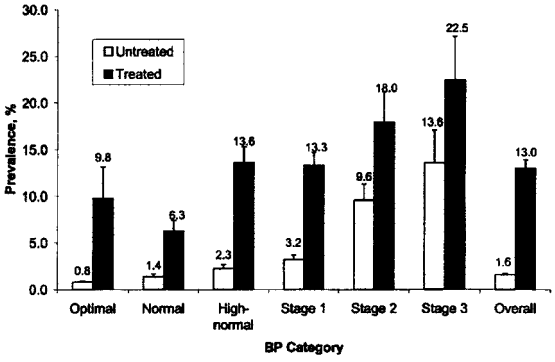


Fig 23. Prevalence of elevated serum creatinine by JNC-VI blood pressure category and self-reported treatment with anti-hypertensive medications (NHANES III). Bars indicate standard errors. Reprinted with permission.[5]

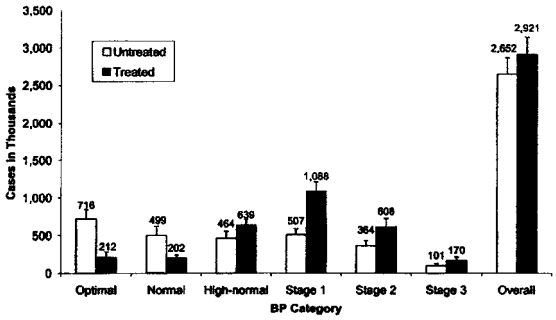


Fig 24. Estimated number of individuals with elevated serum creatinine by JNC-VI blood pressure category and self-reported treatment with anti-hypertensive medications (NHANES III). Bars indicate standard errors. Reprinted with permission.[5]

LIMITATIONS

Unlike other guidelines in Part 6, this guideline is not based on a systematic review of the literature. Another limitation is the lack of large-scale cohort studies and clinical trials correlating blood pressure levels to subsequent loss of GFR and cardiovascular disease events. Since both chronic kidney disease and cardiovascular disease are chronic illnesses, observational studies are subject to confounding by "survival bias," whereby patients with more severe risk factors may not have survived to be entered into the study, thereby minimizing the apparent association between risk factors and outcomes. Thus, clinical trials may be required to determine the optimal level of blood pressure to prevent or slow progression of chronic kidney and development of cardiovascular disease.

A major limitation of cross-sectional studies has been the absence of a clear definition of chronic kidney disease. Since many patients with chronic kidney disease are not detected until late in the course, studies that rely on clinical diagnosis are subject to misclassification. The strong relationship between prevalence of high blood pressure and GFR level observed in NHANES III, irrespective of diagnosis of chronic kidney disease, is especially important in confirming the link between decreased GFR and high blood pressure. However, cross-sectional studies do not permit determination of the causal relationship between these variables. Thus, they cannot determine whether high blood pressure is a cause or a complication of chronic kidney disease, or whether both high blood pressure and decreased GFR are caused by a third factor, such as aging. Nonetheless, the data from both the MDRD Study and NHANES III show a high prevalence of high blood pressure among persons with decreased GFR, justifying the emphasis on monitoring and treatment of high blood pressure in patients with chronic kidney disease.

CLINICAL APPLICATIONS

Detection, evaluation and management of high blood pressure should be the goal for all health care providers for patients with chronic kidney disease. Providers must be aware of lower recommended target levels for blood pressure for patients with chronic kidney disease, specific recommendations for classes of antihypertensive agents, and the role of nonpharmacologic therapy.

IMPLEMENTATION ISSUES

Measuring blood pressure at routine health encounters is widely recommended and practiced. The large number of individuals with blood pressure above the target goal suggests a number of possible obstacles to implementation, such as:

- Limited access to or utilization of health care for many patients with chronic kidney disease
- Inadequate recognition of chronic kidney disease in patients with high blood pressure

Table 74. Recommended Research on High Blood Pressure in Chronic Kidney Disease: Observational Studies

Study Population (Stage of CKD)	Recommended Goals
General population:	Genetic studies to determine reasons for racial differences in high blood pressure, prevalence of chronic kidney disease, and prevalence of cardiovascular disease.
CKD patients: (Stages 1–5)	Determine the prevalence of stages of high blood pressure, as defined by JNC-VI
	Determine the relationship of abnormal ambulatory blood pressure monitoring results (for example, loss of diurnal blood pressure rhythm, "non-dipping") to level of GFR, body water content, and antihypertensive agents.
CKD patients & subgroups[a]: (Stages 1–5)	Determine the relationship of blood pressure level (systolic blood pressure, diastolic blood pressure, mean arterial pressure, and pulse pressure) to mortality and cause of death.
	Determine the relationship of blood pressure level to progression of kidney disease.
	Develop and standard methods to assess body water content.
	Compare blood pressure levels from ambulatory blood pressure monitoring to office and dialysis unit blood pressure levels.
Hemodialysis patients: (CKD Stage 5)	Determine relationships between blood pressure measurements taken at different times (predialysis, postdialysis, intradialysis, ABPM), in different postures (sitting, standing, reclining) and according to different methods (JNC-VI recommendations for office blood pressure measurements, dialysis unit "routine" blood pressure measurement).
	Determine relationship among interdialytic weight gain, intradialytic hypotension, class of antihypertensive agents, and blood pressure levels.
	Determine relationship between changes in blood pressure and serum electrolytes during dialysis with myocardial function and potential for arrhythmias.
	Determine relationships of intradialystic hypotension to coronary heart disease and atherosclerotic disease in other vascular beds (cerebrovascular disease and peripheral vascular disease).
Peritoneal dialysis patients: (CKD Stage 5)	Determine the relationship of residual kidney function, ultrafiltration capacity, and blood pressure levels over time.

[a] "Subgroups" refers to subgroups of the chronic kidney disease population defined by age, gender and race.

Table 75. Recommended Research on High Blood Pressure in Chronic Kidney Disease: Clinical Trials

Study Population (Stage of CKD)	Recommended Goals
CKD patients & subgroups[a]: (Stages 1–5)	Compare the effect of antihypertensive agents on blood pressure control and side effects in different types (diagnosis) of chronic kidney disease.
CKD patients without kidney failure: (Stages 1–4)	Determine the effect of blood pressure level and class of antihypertensive agents on preclinical outcomes of coronary heart disease and left ventricular hypertrophy, and on clinical cardiovascular disease agents.
	Determine the effect of nonpharmacologic therapy (dietary modification, exercise) on body water content, blood pressure control and side effects in different types of chronic kidney disease.
	Compare the effect of antihypertensive agents on progression of different types (diagnosis) of chronic kidney disease.
	Compare the effect of immunousppressive agents on blood pressure levels in kidney transplant recipients.
Hemodialysis patients: (CKD Stage 5)	Determine the effect of class of antihypertensive agents and timing of administration of the antihypertensive agents on intradialytic symptoms.
	Compare control of fluid intake and ultrafiltration vs. antihypertensive agents on blood pressure level and cardiovascular outcomes.
	Determine the feasibility maintaining blood pressure less than 140/90 mm Hg (effect on intradialytic and postdialysis blood pressures).
	Determine the effect of the dialysis membrane and reprocessing techniques on blood pressure level.
	Determine the effect of strategies to minimize intradialytic hypotension on subsequent preclinical and clinical cardiovascular disease outcomes.
Peritoneal dialysis patients: (CKD Stage 5)	Determine the feasibility of maintaining blood pressure less than 140/90 mm Hg.
Hemodialysis & peritoneal dialysis patients: (CKD Stage 5)	Determine the effect of dialysis dose and residual kidney function on blood pressure level.

[a] "Subgroups" refers to subgroups of the chronic kidney disease population defined by age, gender and race.

- Inadequate education of patients and providers regarding lower blood pressure goals, specific classes of antihypertensive agents, and appropriate nonpharmacologic therapy for patients with chronic kidney disease
- Difficulty in attaining blood pressure control in patients with chronic kidney disease.

The high prevalence of earlier stages of chronic kidney disease requires a coordinated national effort by governmental agencies and nongovernmental organizations to address these issues.

RESEARCH RECOMMENDATIONS

A broad set of recommendations for research on high blood pressure in chronic kidney disease was developed by the NKF Task Force on Cardiovascular Disease in Chronic Renal Disease.[248] Recommendations for observational studies are reproduced in Table 74 and for clinical trials in Table 75.

GUIDELINE 8. ASSOCIATION OF LEVEL OF GFR WITH ANEMIA

Anemia usually develops during the course of chronic kidney disease and may be associated with adverse outcomes.

- **Patients with GFR <60 mL/min/1.73 m^2 should be evaluated for anemia. The evaluation should include measurement of hemoglobin level.**
- **Anemia in chronic kidney disease should be evaluated and treated—see K/DOQI Clinical Practice Guidelines for Anemia of Chronic Kidney Disease, Guidelines 1 through 4, as shown in Fig 25.**

BACKGROUND

It is well established that anemia develops in the course of chronic kidney disease and is nearly universal in patients with kidney failure.[264] The development of effective therapeutic options, such as erythropoietin therapy, has provided for the effective treatment of anemia. An earlier K/DOQI clinical practice guideline is devoted to this topic[265,266]; however, that guideline focused primarily on patients treated by dialysis. This guideline addresses anemia in the earlier stages of chronic kidney disease.

Importantly, past guidelines have relied on serum creatinine levels >2 mg/dL as the criterion to test for the presence of anemia. The Work Group recommends that the K/DOQI Anemia guideline be updated to incorporate estimated GFR <60 mL/min/1.73 m^2 to trigger the ascertainment of anemia, rather than the previously cited serum creatinine levels (Fig 25).

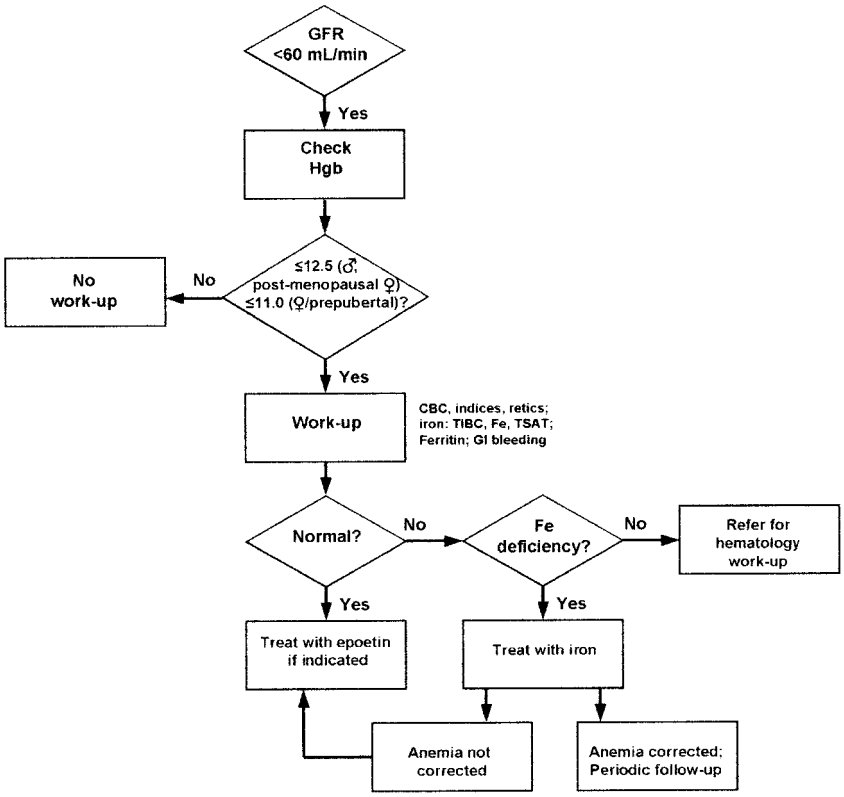


Fig 25. Anemia work-up for patients with chronic kidney disease. Modified and reproduced with permission.[265,266]

RATIONALE

Definition of Anemia

Measures used to assess anemia and its causes include hemoglobin, hematocrit, and iron stores (as measured directly by bone marrow biopsy, or indirectly as measured by serum ferritin, transferrin saturation levels, and percentage of hypochromic red blood cells or reticulocytes). Erythropoietin levels are less useful as a measure of anemia in chronic kidney disease, since it is now well established that they are often not appropriately elevated despite low hemoglobin levels.[267-271]

Measurement of hemoglobin, rather than hematocrit, is the preferred method for assessing anemia. Unfortunately, this issue has been confused due to the use of hematocrit in a number of studies. Hematocrit is a derived value, affected by plasma water, and thus subject to imprecision as a direct measure of erythropoiesis. Measurement of hemoglobin gives an absolute value and, unlike hematocrit, is not affected greatly by shifts in plasma water, as may occur with diuretics or with dialysis therapy. Hemoglobin levels are directly affected by lack of erythropoietin production from the kidney and thus serve as a more precise measurement of erythropoiesis.

While decreased hemoglobin often accompanies chronic kidney disease, there is no quantitative definition of anemia in chronic kidney disease, since "acceptable" (normal) hemoglobin levels have not been defined for patients with kidney disease. Instead, anemia is defined according to physiological norms. All patients with chronic kidney disease who have hemoglobin levels lower than physiological norms are considered anemic.

The definition of anemia in chronic kidney disease is further complicated by gender differences in hemoglobin levels. In the normal population, hemoglobin levels vary between genders and also as a function of menopausal status. The World Health Organization defines anemia to be that level of hemoglobin and gender-determined normal ranges without reference to age or menopausal status.[272] Thus, for males, anemia is defined as hemoglobin level $<$13.0 g/dL, while in women, anemia is defined as hemoglobin level $<$12.0 g/dL. The WHO is in the process of updating these definitions to expand and refine them with specific levels in pregnant women and children of different ages. In most studies of anemia related to the level of kidney function, these issues have not been taken into account.

The operational definition of anemia in patients with kidney disease has also been influenced by health policy. In the past, national reimbursements (such as Medicare and Medicaid in the United States) have required the attainment of specific levels of hemoglobin or hematocrit, leading investigators and clinicians to define anemia relative to those regulatory levels. As stated in the European Best Practice Guidelines for the Management of Anaemia,[273] it is important to define anemia relative to physiological norms rather than payment rules.

Some studies have arbitrarily defined the "anemia" of kidney disease as a hemoglobin level below some discretionary level (eg, 10 g/dL) that is well below the normative values in the general population. The low hemoglobin level that is often seen in chronic kidney disease should not lead to the acceptance of lower than normal hemoglobin levels as appropriate in patients with chronic kidney disease.

Strength of Evidence

Anemia develops during the course of chronic kidney disease (R). Lower hemoglobin may result from the loss of erythropoietin synthesis in the kidneys and/or the presence of inhibitors of erythropoiesis. Numerous articles document the association of anemia with kidney failure and describe its various causes.[267,268,274-276] The severity of anemia in chronic kidney disease is related to the duration and extent of kidney failure. The lowest hemoglobin levels are found in anephric patients and those who commence dialysis at very severely decreased levels of kidney function.[271,277,278]

Anemia is associated with worse outcomes in chronic kidney disease (R). As yet it is undetermined whether the presence of anemia in chronic kidney disease directly worsens prognosis or whether it is a marker for the severity of other illnesses. Definitive studies have not been concluded. The available evidence, consisting of large database analysis and population studies, clearly show that low hemoglobin levels are associated with higher rates of hospitalizations,

cardiovascular disease, cognitive impairment, and other adverse patient outcomes, including mortality.[279-284]

Erythropoietin deficiency is the primary cause of anemia in chronic kidney disease (R). Anemia in patients with chronic kidney disease is due to a number of factors, the most common of which is abnormally low erythropoietin levels. Other causes include: functional or absolute iron deficiency, blood loss (either occult or overt), the presence of uremic inhibitors (eg, parathyroid hormone, spermine, etc), reduced half life of circulating blood cells, deficiencies of folate or Vitamin B_{12}, or some combination of these with a deficiency of erythropoietin.[267-269,274,275] Patients with kidney disease may have concurrent underlying hematological problems such as thalassemia minor, sickle cell disease, or acquired diseases such as myelofibrosis or aplastic anemia.

The causative role of erythropoietin deficiency in anemia of chronic kidney disease includes: (1) anemia is responsive to treatment with erythropoietin in all stages of chronic kidney disease; and (2) in patients with chronic kidney disease, circulating levels of erythropoietin are not sufficient to maintain hemoglobin within the normal range. North American (United States and Canada) and European studies have demonstrated these points.[270,271,282,285-287]

Onset and severity of anemia are related to the level of GFR; below a GFR of approximately 60 mL/min/1.73 m^2, there is a higher prevalence of anemia (Tables 76 and 77 and Figs 26, 27, 28, and 29) (C, S). Studies reviewed for the purposes of this guideline include those of patients with chronic kidney disease prior to dialysis, those with kidney transplants, and those on dialysis.

The reviewed literature spans almost 30 years

Table 76. Hemoglobin and Kidney Function

Author, Year	No. of Subjects	Applicability	GFR Range (mL/min/1.73 m^2) 0 30 60 90 120	Results*/ Mean Level	Quality
Levin,[288] 1999	318	↑↑↑		↑	●
Taralov,[289] 1998	63	↑↑	S_{Cr} 5.1 mg/dL	↑	●
Clyne,[290] 1993	58	↑↑		⇧	●
Ishimura,[291] 1998	40	↑↑	S_{Cr} 2–8 mg/dL	↑	●
Nankivell,[141] 1995	123	↑		↑	○
de Klerk,[292] 1982	99	↑		⇧	○
Urabe,[293] 1987	17	↑	S_{Cr} 7–15 mg/dL	⇔	○
Silverberg,[294] 1996	33	↑↑		10.0 g/dL	●
Lin,[295] 1996	51	↑↑		12.5 g/dL	○
Clyne,[296] 1994	12	↑		8.9 g/dL	○
Portoles,[297] 1997	11	↑		9.0 g/dL	○
Dimitrakov,[298] 1994	6	↑	S_{Cr} 4.5±0.4 mg/dL	7.6 g/dL	○

Unshaded studies reported the strength of association between the outcome measure (in this case, hemoglobin) and kidney function; shaded studies reported mean or median levels of the outcome measure in the study sample.

* ↑ = higher GFR associated with higher hemoglobin (statistically significant);
⇧ = higher GFR associated with higher hemoglobin;
⇔ = GFR *not* associated with hemoglobin.

Table 77. Hematocrit and Kidney Function

Author, Year	No. of Subjects	Applicability	GFR Range (mL/min/1.73 m²) 0 30 60 90 120	Results*/ Mean Level	Quality
Klahr,[299] 1995	840	♦♦♦		⬆	●
Radtke,[268] 1979	194	♦♦		⬆	●
Howard,[300] 1989	106	♦♦		⬆	●
Lim,[301] 1990	26	♦♦	S_{Cr} 2–12 mg/dL	⬆	○
Besarab,[302] 1985	102	♦	S_{Cr} 1.5–2.1 mg/dL	⇧	○
Brod,[303] 1967	17	♦		⇧	○
Urabe,[293] 1987	17	♦	S_{Cr} 7–15 mg/dL	⇔	○
Silverberg,[294] 1996	33	♦♦		30%	●
Roth,[304] 1994	83	♦		27%	●
Kuriyama,[305] 1997	66	♦♦		32%	○
Lin,[295] 1996	51	♦♦		35%	○
Portoles,[297] 1997	11	♦		26%	○
Hayashi,[306] 2000	9	♦	S_{Cr} 6.2 ±0.7 mg/dL	24%	○
Schwartz,[307] 1991	7	♦		29%	○
Dimitrakov,[298] 1994	6	♦	S_{Cr} 4.5 ±0.4 mg/dL	23%	○

* ⬆ = higher GFR associated with higher hematocrit (statistically significant);
⇧ = higher GFR associated with higher hematocrit;
⇔ = GFR *not* associated with hematocrit.

of investigation and describes the clinical findings of researchers as they explore the relationships between hemoglobin and kidney function (Tables 76 and 77). The majority of available data have been derived from studies of small sample size, most of which are cross-sectional studies or baseline data from clinical trials of variable size and robustness. These studies are predominantly of only moderate or modest quality from a methodological standpoint. The consistency of the information they provided does, however, indicate a trend toward lower hemoglobin levels at lower levels of GFR and a variability in hemoglobin levels across GFR levels.

In 12 of the 22 studies reviewed, there was an association between the level of hemoglobin or hematocrit and the selected measure of kidney function. Data obtained from the NHANES III analysis (Fig 26) demonstrates an association between hemoglobin and level of GFR at GFR levels <90 mL/min/1.73 m^2. While the increase in prevalence of anemia is most notable in the population studied at GFR levels <60 mL/min/1.73 m^2, anemia can be present in patients with higher GFR levels. Due to the sparcity of data points at values <30 mL/min/1.73 m^2 in the NHANES III database, the Canadian Multicentre Study[288] was utilized to demonstrate trends in a large cohort of patients prior to dialysis (Fig 28). Note in Fig 29 the increase in prevalence of anemia at lower levels of GFR, but the existence of up to 20% of patients with anemia at higher, though still abnormal levels of GFR (30 to 44 mL/min/1.73 m^2). Thus, the NHANES III data

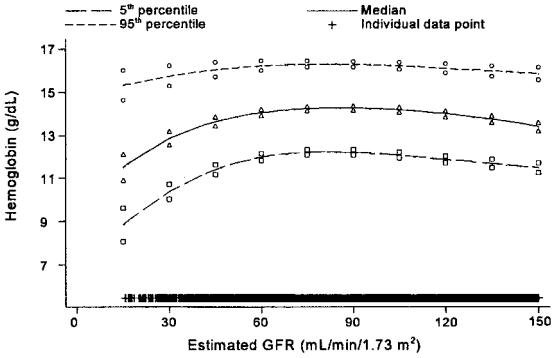


Fig 26. Blood hemoglobin percentiles by GFR adjusted to age 60 (NHANES III). Median and 5th and 95th percentiles of hemoglobin among adult participants age 20 years and older in NHANES III, 1988 to 1994. Values are adjusted to age 60 years using a polynomial quantile regression. The estimated GFR for each individual data point is shown with a plus sign (+) near the abscissa. 95% confidence intervals at selected levels of estimated GFR are demarcated with triangles, squares, and circles.

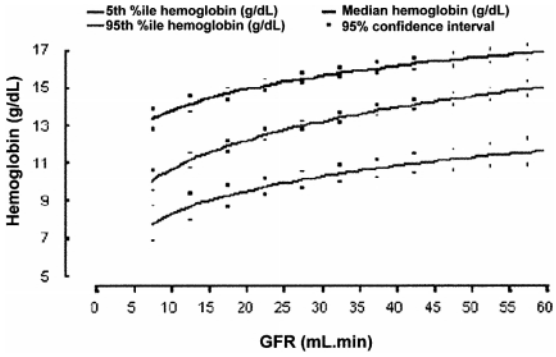


Fig 28. Hemoglobin percentiles by GFR. These data are based on the results of 446 patients enrolled in the Canadian Multicentre Longitudinal Cohort study of patients with chronic kidney disease. All patients were referred to nephrologists between 1994 and 1997. No patient was receiving erythropoietin therapy at the time of enrollment, and no patient had an AV fistula. Adapted and reprinted with permission.[288]

are consistent with data derived from populations with kidney disease and lower GFR[288] (Figs 28 and 29).

Published studies cited in Tables 76 and 77 demonstrate a variability in the levels of hemoglobin or hematocrit at each level of kidney function, whether assessed by serum creatinine concentration, creatinine clearance, or GFR. These observations underscore the need to measure hemoglobin levels in every individual with GFR <60 mL/min/1.73 m^2 and to individualize the assessment of anemia. The population-based trend toward lower hemoglobin levels as GFR falls does not yield a predictable progression that can be applied to individual patients. Thus, anemia should be considered in some patients with chronic kidney disease and GFR >60 mL/min/1.73 m^2.

Erythropoietin levels are not consistently associated with the level of GFR (Table 78) (C). Erythropoietin levels in patients with chronic kidney disease have not been well characterized in studies to date and do not appear to be directly related to level of kidney function. The majority of studies have been performed in patients al-

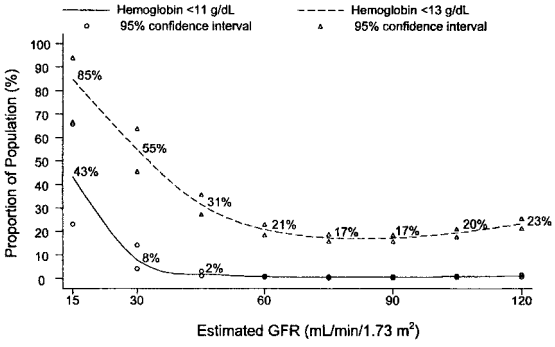


Fig 27. Adjusted prevalence in adults of low hemoglobin by GFR (NHANES III). Predicted prevalence of hemoglobin <11 and <13 g/dL among adult participants age 20 years and older in NHANES III, 1988 to 1994. Values are adjusted to age 60 years using a polynomial regression. 95% confidence intervals are shown at selected levels of estimated GFR.

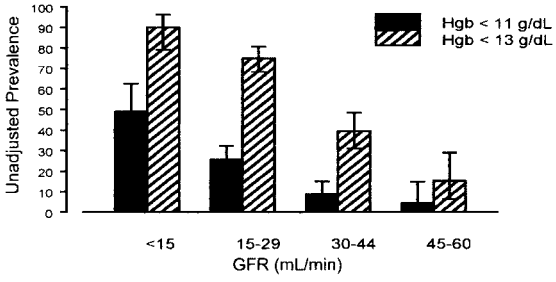


Fig 29. Prevalence of low hemoglobin by GFR category. These data are based on the results of 446 patients enrolled in the Canadian Multicentre Longitudinal Cohort study of patients with chronic kidney disease. All patients were referred to nephrologists between 1994 and 1997. No patient was receiving erythropoiten therapy at the time of enrollment, and no patient had an AV fistula. Adapted and reprinted with permission.[288]

Table 78. Erythropoietin Level and Kidney Function

Author, Year	No. of Subjects	Applicability	GFR Range	Results*	Quality
Besarab,[310] 1987	65	⇑⇑	ND	⇔	○
Urabe,[293] 1987	17	⇑	S_{Cr} 7–15 mg/dL	⇔	○

* ⇔ = GFR *not* associated with erythropoietin.

ready receiving dialysis, though some studies describe the relationship of erythropoietin levels to GFR in diabetics and in patients not on dialysis.[275,308,309]

The consistent finding apparent from these studies is that, for any given level of kidney function and anemia, the erythropoietin levels are lower in individuals with kidney disease than in those with anemia but normal kidney function.

The interpretation of these findings is that patients with kidney disease, as compared to normal individuals, do not have an appropriate rise in the levels of erythropoieten in the presence of anemia; while levels may be higher than non-anemic chronic kidney disease patients, the rise in erythropoietin levels is not commensurate with that seen in patients with the same degree of anemia but without kidney disease. Table 77 shows the paucity of data in this area and the weakness of the association demonstrated by published studies between erythropoiten levels and level of kidney function.

Measures of iron stores, including ferritin and transferrin saturation, are not consistently associated with the level of GFR (Tables 79 and 80) (C). Several measures of iron stores have been studied in patients with kidney disease. Most of these measures, unlike bone marrow biopsy, do not directly quantify the amount of iron available for use in erythrocyte synthesis, relying instead on indirect or surrogate measures. Ferritin levels in patients with reduced GFR may represent total body iron status, or they may simply be markers of inflammation. Given the "chronic inflammatory state" that may characterize chronic kidney disease, ferritin levels are not useful in measuring iron stores, nor in predicting the relation of hemoglobin to kidney function.

Transferrin saturation, in combination with serum iron and ferritin levels, may be helpful in diagnosing functional iron deficiency—just as low serum ferritin levels are helpful in diagnosing iron deficiency anemia.[311,312] However, there is little correlation of iron measurements with stages of kidney disease.

LIMITATIONS

This analysis is limited by a lack of data about the relationship of levels of hemoglobin and kidney function in a truly representative sample of patients with chronic kidney disease. Many of the published studies describe patients entered into clinical trials or seen by nephrologists. The reasons for these differences are incompletely studied but noted in conventional texts and review articles.[277,313]

Interestingly, specific subgroups of patients (such as those with polycystic kidney disease) may have erythropoietin synthesis that is better preserved than other subgroups (such as diabetics). In the subgroup of patients who have kidney

Table 79. Ferritin and Kidney Function

Author, Year	No. of Subjects	Applicability	GFR Range (mL/min/1.73 m²) 0 30 60 90 120	Results*/ Mean Level	Quality
Taralov,[289] 1998	63	⇑⇑	S_{Cr} 5.1 mg/dL	⇑	●
Lin,[285] 1996	51	⇑⇑		296 µg/L	○
Dimitrakov,[298] 1994	6	⇑	S_{Cr} 4.5±0.4 mg/dL	247 µg/L	○

* ⇑ = higher GFR associated with higher ferritin (statistically significant).

Table 80. Miscellaneous Hematological Measures and Kidney Function

Author, Year	No. of Subjects	Applicability	GFR Range (mL/min/1.73 m²) 0 30 60 90 120	Results*/ Mean Level	Quality
Taralov,[289] 1998	63	↑↑	S_{Cr} 5.1 mg/dL	↑	●
Silverberg,[294] 1996	33	↑↑		Iron saturation = 22%	●
Lin,[295] 1996	51	↑↑		Transferrin saturation = 31%	○
Dimitrakov,[298] 1994	6	↑	S_{Cr} 4.5±0.4 mg/dL	Transferrin = 2.8 g/L Fe = 72 mg/dL	○

* ↑ = higher GFR associated with higher iron (statistically significant).

transplants, there are multiple causes for anemia in addition to decreased kidney function. The use of immunosuppressive agents or other medications, or chronic inflammation due to transplant rejection, may further confound the assessment of the etiology of declining hemoglobin. However, it is clear that at given levels of compromised GFR, kidney transplant patients do demonstrate reduced levels of hemoglobin, consistent with findings in patients with native diseased kidneys, and with those who have impaired kidney function.[310]

Another limitation of the current analysis is the variety (and lack of precision) of methods by which kidney function was measured in studies that assessed hemoglobin in patients with chronic kidney disease. Methods used included: measured GFR (iothalamate or other methods), calculated GFR (using different equations), measured or calculated creatinine clearance (using different equations). It is therefore difficult to determine whether the variability in hemoglobin at levels of kidney function is due to variability in measurements of kidney function or to variability associated with chronic kidney disease itself. While true variability between patients is the more likely possibility, the magnitude of variability is unknown.

CLINICAL APPLICATIONS

Available data permit the description of mean levels of hemoglobin (with wide standard deviations) at different levels of GFR and support the following recommendations. Physicians treating patients with chronic kidney disease should:

- Follow hemoglobin levels over time in all individuals with chronic kidney disease and expect some degree of decline over time as kidney function worsens
- Evaluate anemia in all patients with GFR <60 mL/min/1.73 m^2
- Assess the relationship of anemia to the patient's symptoms and findings and the impact of anemia on the patient's comorbid conditions and other complications of decreased kidney function
- As in anemia from any cause, treatments appropriate to the etiology of the anemia (iron or other supplement deficiency) should be implemented. The issues of timing of intervention and specific target of hemoglobin are beyond the scope of this guideline.

These recommendations are consistent with published K/DOQI Clinical Practice Guidelines on Anemia of Chronic Kidney Disease.[266] While there are no "normal"/expected values of hemoglobin at any specific level of GFR, available data suggest that individual patients do trend toward a fall in hemoglobin as kidney function declines. The characterization of severity of anemia for any individual with chronic kidney disease should be made in light of changes in hemoglobin from previous levels. The decline in hemoglobin is most likely associated with a reduction in erythropoietin effectiveness or production, which accompanies the decline in GFR.

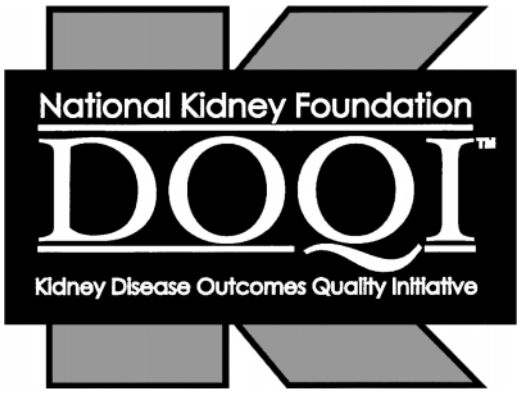
Treatment and assessment recommendations are beyond the scope of this guideline but are provided in the K/DOQI Clinical Practice Guidelines on Anemia of Chronic Kidney Disease[266] and the European Best Practice Guidelines for

the Management of Anaemia in Patients with Chronic Renal Failure.[273]

RESEARCH RECOMMENDATIONS

Clearly, more information is needed on hemoglobin levels in chronic kidney disease—especially in patients in the early stages of kidney disease and as kidney function declines. Future studies should include:

- Evaluation of the relationships between erythropoietin levels, hemoglobin and iron stores in patients with chronic kidney disease at each stage of the disease
- Description of changes in these hematological parameters in specific subgroups, such as diabetics and patients with failing transplant grafts
- Evaluation of the impact of treatment of anemia in stages of kidney disease prior to dialysis (CKD Stages 1-4) on kidney function decline, cardiac function, and general well-being
- Economic evaluations of therapeutic strategies which include maintenance of hemoglobin versus correction from low levels at different stages of chronic kidney disease.



GUIDELINE 9. ASSOCIATION OF LEVEL OF GFR WITH NUTRITIONAL STATUS

Protein energy malnutrition develops during the course of chronic kidney disease and is associated with adverse outcomes. Low protein and calorie intake is an important cause of malnutrition in chronic kidney disease.

- **Patients with GFR <60 mL/min/1.73 m^2 should undergo assessment of dietary protein and energy intake and nutritional status—see K/DOQI Clinical Practice Guidelines for Nutrition in Chronic Renal Failure (CRF), Guidelines 23 and 26:**

Guideline 23. Panels of Nutritional Measures for Nondialyzed Patients: "For individuals with CRF (GFR <20 mL/min) protein-energy nutritional status should be evaluated by serial measurements of a panel of markers including at least one value from each of the following clusters:

(1) Serum albumin;
(2) Edema-free actual body weight, percent standard (NHANES II) body weight, or subjective global assessment (SGA); and
(3) Normalized protein nitrogen appearance (nPNA) or dietary interviews and diaries. (Evidence and Opinion)"

Guideline 26. Intensive Nutritional Counseling for Chronic Renal Failure: "The nutritional status of individuals with CRF should be monitored at regular intervals."

- **Patients with decreased dietary intake or malnutrition should undergo dietary modification, counseling, and education or specialized nutrition therapy—see K/DOQI Clinical Practice Guidelines for Nutrition in Chronic Renal Failure (CRF), Guidelines 24 and 25:**

Guideline 24. Dietary Protein Intake for Nondialyzed Patients: "For individuals with chronic renal failure (GFR <25 mL/min) who are not undergoing maintenance dialysis, the institution of a planned low-protein diet providing 0.60 g protein/kg/d should be considered. For individuals who will not accept such a diet or who are unable to maintain adequate dietary energy intake with such a diet, an intake of up to 0.75 g protein/kg/d may be prescribed. (Evidence and Opinion)."

Guideline 25. Dietary Energy Intake (DEI) for Nondialyzed Patients: "The recommended DEI for individuals with chronic renal failure (GFR <25 mL/min) who are not undergoing maintenance dialysis is 35 kcal/kg/d for those who are younger than 60 years old and 30-35 kcal/kg/d for individuals who are 60 years of age or older. (Evidence and Opinion)."

BACKGROUND

Anorexia is evidenced by decreased dietary protein intake (DPI) and decreased dietary energy intake (DEI), which are hallmarks of kidney failure (K/DOQI Clinical Practice Guidelines for Nutrition in Chronic Renal Failure,[75] Guideline 6). As limitation of protein intake reduces the accumulation of toxic substances derived from the metabolism of protein, decreased DPI may be viewed as adaptive in patients with kidney failure. However, decreased DPI is also associated with worsening of indices of nutritional status. Thus, the overall outcome of this adaptive process may be the increased prevalence of protein energy malnutrition (PEM) in patients with chronic kidney disease.

The stage of chronic kidney disease at which decreased dietary nutrient intake and associated PEM become prevalent has not been adequately documented, due in part to the fact that no single measure provides a complete overview of nutritional status. The optimal monitoring of protein-energy nutritional status requires the collective evaluation of multiple parameters (ie, assessment of visceral protein, muscle mass or somatic protein, body composition). As a result, data for appropriate assessment of nutritional status in patients with chronic kidney disease have not been adequately collected and often the onset

and progression of malnutrition is obscured by the progressive loss of kidney function. This guideline provides evidence on the association of the level of GFR with dietary intake and nutritional status and provides recommendations on how to approach this specific complication of chronic kidney disease.

RATIONALE

Markers of Protein-Energy Malnutrition

PEM is characterized by the insidious loss of body fat and somatic protein stores, diminished serum protein concentrations, and poor performance status and function. Serum albumin, serum prealbumin, and serum transferrin levels are used to measure visceral protein. Anthropometry and dual-energy x-ray absorptiometry assess somatic protein and fat stores. In addition, edema-free weight, body mass index (BMI), and subjective global assessment (SGA) are valid and clinically useful tools for overall nutritional assessment.

Serum albumin concentration, even when only slightly less than 4.0 g/dL, is one of the most important markers of PEM in patients with chronic kidney disease. It is a very reliable indicator of visceral protein, although its concentration is also affected by its rate of synthesis and catabolism (half-life 20 days), which is altered negatively in the presence of inflammation.[314] The distribution of albumin between extracellular and intravascular spaces may be variable depending on the etiology of kidney disease, magnitude of proteinuria, and the state of extracellular fluid volume. In chronically malnourished patients, albumin tends to shift out of the intravascular compartment.

Several markers of visceral protein, other than albumin, have a shorter half-life and may be useful markers of early malnutrition. Among these are serum transferrin (half-life 8 days) and serum pre-albumin (half-life 2 days).[315] Iron stores affect serum transferrin, while pre-albumin is excreted by the kidneys and its concentration can be falsely elevated in patients with advanced kidney disease. All these markers are also affected by the presence of inflammation.

Anthropometry (edema-free weight, BMI, assessment of arm fat and muscle) has been used to estimate body composition and nutritional adequacy. Reproducibility of anthropometry measurements is poor and is dependent upon the skill of the observer. SGA has been proposed as an easy, useful, and clinically valid method for nutritional assessment. SGA includes subjective data (disease state, weight changes), indicators of poor nutritional status (appetite, food intake, gastrointestinal symptoms), and the clinical judgment of the clinician. The limitation of SGA is its reliance on subjective data. There are no studies which correlate anthropometric measurements or SGA with clinical outcome in patients with chronic kidney disease.

Serum bicarbonate concentration (also measured as total carbon dioxide content or CO_2), as a measure of acid-base balance, has been used to assess malnutrition in chronic kidney disease. Studies show that uremic acidosis causes an increase in protein degradation. Correction of acidosis is accompanied by a decrease in protein tissue breakdown.[316]

Assessment of nutrient intake can be useful in identifying PEM and several measures of dietary intake have been utilized in patients with chronic kidney disease. These include measurement of protein equivalent of total nitrogen appearance (PNA) as a marker of dietary protein intake, measurement of basal energy expenditure (BEE) as a measure of dietary energy needs, and dietary interviews or diaries as markers of overall intake. Additionally, total serum cholesterol can be a useful marker for energy intake, but not for protein intake.

The challenge for the clinician is to appropriately monitor the nutritional indices in patients with chronic kidney disease. While each marker has its own advantage in terms of precision and predictability, it is recommended that these markers be used in a complementary fashion to optimize assessment of patients with chronic kidney disease and to tailor specific interventions.[75]

It is also important for the clinician to educate patients about a proper diet, since hyperphosphatemia, hyperkalemia, and metabolic acidosis may develop during chronic kidney disease.

Medical Nutrition Therapy and Nutrition Counseling

As of January 2002, Medicare will provide payment for medical nutrition therapy (MNT) for patients with chronic kidney disease.[317]

"Medical nutrition therapy involves the assessment of the nutritional status of patients with a condition, illness, or injury that puts them at risk. This includes review and analysis of medical and diet history, laboratory values, and anthropometric measurements. Based on the assessment, nutrition modalities most appropriate to manage the condition or treat the illness or injury are chosen and include the following:

- *Diet modification, counseling, and education leading to the development of a personal diet plan to achieve nutritional goals and desired health outcomes.*
- *Specialized nutrition therapies including supplementation with medical foods for those unable to obtain adequate nutrients through food intake only; enteral nutrition delivered via tube feeding into the gastrointestinal tract for those unable to ingest or digest food; and parenteral nutrition delivered via intravenous infusion for those unable to absorb nutrients."*

Presently, it is proposed that patients will be eligible to receive reimbursement for medical nutrition therapy if they have GFR 15 to 50 mL/min/1.73 m^2, or if they have received a kidney transplant within the previous 6 months. These criteria are roughly equivalent to patients with CKD Stages 3-4 and Stage 5 who do not yet require dialysis. Most patients with CKD Stage 5 who are treated by dialysis are eligible for medical nutrition therapy from their dialysis providers.

Strength of Evidence

PEM develops during the course of chronic kidney disease (R). When compared to the demographically adjusted general population, dialysis patients experience greater signs and symptoms of wasting, malnutrition, morbidity, and mortality. It is estimated that 50% to 70% of dialysis patients suffer from PEM.[314] Abnormalities in nutritional markers are common and include decreased serum proteins, lower body mass as assessed by anthropometric measurements and SGA, and decreased nutrient intake. Reasons for PEM include disturbances in protein and energy metabolism, hormonal derangements, anorexia, and nausea and vomiting related to uremic toxicity. Comorbid conditions such as diabetes, vascular disease, and superimposed infections and inflammation are contributory.[318]

Malnutrition is associated with worse outcomes in chronic kidney disease (R). Among maintenance dialysis patients, PEM has been recognized as one of the most significant predictors of adverse outcomes. Risk of hospitalizations and mortality is inversely correlated to nutritional markers.[319] Recently, attention has focused on the characteristics of patients with chronic kidney disease at the time they begin maintenance dialysis. Studies have suggested that apart from the severity of uremic symptoms as well as the biochemical findings related to the extent of metabolic and hormonal abnormalities, the nutritional status of the patient at the initiation of dialysis is a clinically significant risk factor for subsequent clinical outcomes (morbidity and mortality) on dialysis.[320,321] The association between nutrition intake or status and clinical outcome does not prove a causal relationship. It is possible that comorbid conditions independently impair both nutritional intake or status and increase morbidity and mortality. In addition studies suggest that a combined state of poor nutritional status and inflammation predispose patients with chronic kidney disease to poor clinical outcomes.[322,323]

Low protein and calorie intake is an important cause of malnutrition in chronic kidney disease (R). While there are possibly multiple factors that contribute to the development of PEM in chronic kidney disease, low protein and calorie intake (decreased from usual intake) are certainly important contributors in this catabolic process. This relationship is evident from multiple studies, which show a strong relationship between the amount of dietary intake of nutrients, especially protein intake, and the stage of malnutrition in patients with chronic kidney disease.[324,325] Concentrations of serum albumin and transferrin, edema free weight, and percent lean body mass have all been directly related to dietary protein intake in patients with chronic kidney disease.

The mechanism by which chronic kidney disease leads to this decline in nutrient intake has not been defined. Accumulation of uremic toxins due to loss of kidney function is a potential

explanation. Metabolic and hormonal derangements predispose patients with chronic kidney disease to decreased appetite and dietary nutrient intake.[326,327] Specific comorbid conditions, such as diabetes mellitus, cardiovascular disease, and depression, can facilitate the worsening of decreased nutrient intake in patients with chronic kidney disease. The mechanisms associated with these conditions are multiple and include gastrointestinal abnormalities, decreased appetite, effects of concomitant medication use, and role of inflammation.

Other causes of malnutrition in chronic kidney disease (R). Several factors other than low protein and calorie intake can also predispose chronic kidney disease patients to malnutrition. These include several hormonal and metabolic derangements related to loss of kidney function. Metabolic acidosis is commonly seen in chronic kidney disease patients and shown to be associated with increased protein catabolism in these patients. Specifically, the degradation of the essential, branched-chain amino acids and muscle protein is stimulated during metabolic acidosis. Further, metabolic acidosis suppresses albumin synthesis.[328] Worsening kidney function is also associated with resistance to insulin, growth hormone and insulin-like growth factor 1, all of which are known to be anabolic hormones. Of note, these abnormalities are most prominent in pediatric chronic kidney disease patients with apparent growth failure.[329-331]

Recent studies point to the increased concentrations of proinflammatory cytokines and acute phase reactants in chronic kidney disease patients.[323,332] Analysis of the data from NHANES III demonstrates increasing C-reactive protein concentrations as GFR decreases.[333] Thus, available evidence suggests a chronic inflammatory state in chronic kidney disease patients, especially for patients in Stages 3 to 5. The metabolic and nutritional effects of chronic inflammation are many and include anorexia, increased skeletal muscle protein breakdown, increased whole body protein catabolism, cytokine-mediated hypermetabolism, and disruption of the growth hormone and IGF-1 axis leading to decreased anabolism.[334-336] These findings suggest that chronic inflammation observed in chronic kidney disease patients is an important causative factor for poor nutritional status observed in these patients.

The level of dietary intake of protein and energy intake is related to the level of GFR; below a GFR of approximately 60 mL/min/1.73 m^2, there is a higher prevalence of reduced dietary protein and energy intake (Tables 81 and 82 and Fig 30) (C, S). One of the most significant clinical indicators of kidney failure is an apparent decrease in appetite. Spontaneous decrease in dietary protein and energy intake can be regarded as an early index of uremia. This begins to occur when GFR falls below 60 mL/min/1.73 m^2. As protein and calorie intake decline, markers of nutrition health indicate worsening nutritional status.

Table 81. Daily Calorie Intake and Kidney Function

Author, Year	No. of Subjects	Applicability	GFR Range (mL/min/1.73 m^2) 0 30 60 90 120	Results/ Mean Level	Quality
Kopple,[324] 2000	1,785	↑↑↑		↑	●
Kopple,[338] 1989	89	↑↑		⇔ (men) ↑ (women)	●
Chauveau,[343] 1999	10	↑		27.8 Kcal/kg/d	○
Williams,[344] 1991	6	↑		38.3 Kcal/kg/d	○

Unshaded studies reported the strength of association between the outcome measure (in this case, daily calorie intake) and kidney function; shaded studies reported mean or median levels of the outcome measure in the study sample.

* ↑ = higher GFR associated with higher daily caloric intake (statistically significant);
⇔ = GFR *not* associated with daily caloric intake.

Table 82. Daily Protein Intake and Kidney Function

Author, Year	No. of Subjects	Applicability	GFR Range (mL/min/1.73 m^2) 0 30 60 90 120	Results*/ Mean Level	Quality
Kopple,[324] 2000	1,785	†††		↑	●
Ikizler,[325] 1995	90	†††		↑	●
Kopple,[338] 1989	89	††		↑	●
Coggins,[339] 1994	33	††		↑	●
Park,[340] 1997	64	†††		↑	⊙
Pollock,[341] 1997	439	††		↑	○
Aparicio,[345] 2000	239	††		0.84 g/kg/d	●
Walser,[346] 1993	16	††		0.82 g/kg./d	●
Mazouz,[347] 1999	49	††		0.87 g/kg/d	⊙
Chauveau,[343] 1999	10	†		0.78 g/kg/d	⊙
Williams,[344] 1991	6	†		82.2 g/d	⊙

* ↑ = higher GFR associated with higher daily protein intake (statistically significant).

K/DOQI Nutrition Guideline 24 recommends consideration of a protein intake of 0.60 g/kg/d for individuals with GFR <25 mL/min (corresponding approximately to CKD Stages 4-5), but does not address recommendations for patients with higher GFR. The recommended dietary allowance (RDA) of protein for normal adults is 0.75 g/kg/d. The MDRD Study was inconclusive regarding the benefits of protein restriction on kidney disease progression (see CKD Guideline 13), but there was no evidence of a beneficial effect from DPI higher than the RDA. A DPI of 0.75 g/kg/d therefore appears reasonable for patients with CKD Stages 1-3 (in the absence of evidence of malnutrition), but data are inconclusive, and individualized decision-making is advised. Patients with DPI less than approximately 0.75 g/kg/d should have more close monitoring of nutritional status.

K/DOQI Nutrition Guideline 25 recommends age-dependent DEI intakes of 30 to 35 kcal/kg/d for individuals with GFR <25 mL/min (corresponding approximately to CKD Stages 4-5), but does not address recommendations for patients with higher GFR. The RDA for energy intake in normal adults depends on energy expenditure. Average energy intake in adults in the United States is less than that recommended in the K/DOQI Nutrition Guideline. The rationale for higher DEI in patients with GFR <25 mL/min is based on studies demonstrating more efficient nitrogen utilization at higher energy intakes. For patients with CKD Stages 1-3, it would be reasonable to recommend higher energy intakes only if they have abnormally low body weight or show other signs of malnutrition.

Patients with DPI less than the RDA (0.75 g/kg/d) should be targeted for frequent follow-up to monitor nutritional status more closely. Some studies indicate that intensive nutrition counseling may help maintain calorie intake and to preserve markers of good nutrition as GFR declines.[299,324,325,337-342]

The onset and severity of PEM is related to the level of GFR; below a GFR of approximately 60 mL/min/1.73 m^2, there is a higher prevalence of impaired nutritional status (C, S).

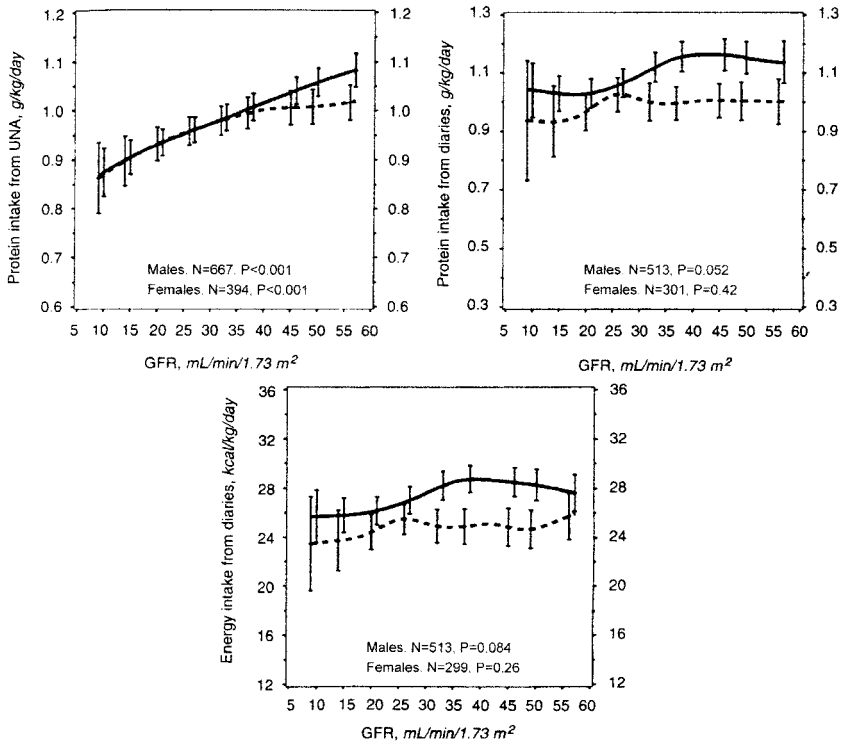


Fig 30. Association of dietary intake and GFR in the MDRD Study. Mean levels of protein and energy intake as a function of GFR based on 24-hour urine collections and diet diaries (males, solid lines; females, dashed lines). Data depict MDRD Study enrollees not on restricted diets. Abbreviation: UNA, urea nitrogen appearance. Reprinted with permission.[324]

K/DOQI Nutrition Guideline 23 states that protein-energy nutritional status should be evaluated by serial measurements for individuals with GFR <20 mL/min.[75] An updated literature review supports the recommendation that evaluations of nutritional status should begin when GFR falls below approximately 60 mL/min/1.73 m^2. Population studies show that albumin begins to decline once GFR reaches this level.[333] Other markers of nutritional status at this level of kidney function have not been as well studied.

K/DOQI Nutrition Guideline 23 recommends a panel of nutrition measures for evaluation of nutrition status in nondialyzed patients which includes serum albumin, body weight, subjective global assessment and assessment of protein intake through nPNA or dietary interviews. Other markers of nutritional status (eg, serum total proteins, serum prealbumin, serum transferrin, serum total bicarbonate, serum total cholesterol, and serum lipids) appear to be related to the level of GFR.

The calculation of standard body weight (SBW) requires a formula that uses elbow breadth to determine the patient's frame size. For many clinicians, this measurement is not feasible. The calculation of healthy weight range can be made with the simpler Body Mass Index (BMI) formula:

$$\text{BMI} = \frac{\text{Weight (kg)}}{\text{Height (m)}^2}$$

It is recommended that the BMI of maintenance dialysis patients be maintained in the upper 50th percentile for normal individuals, which would mean a BMI for men and women no lower than approximately 23.6 to 24.0 kg/m^2. This recommendation also appears appropriate for chronic kidney disease patients with significant GFR reductions (Stages 3-5)—see K/DOQI Nutrition Guideline, Appendix VII.

K/DOQI Nutrition Guideline 26 recommends monitoring of nutritional status at 1- to 3-month intervals in patients with GFR <20 mL/min. It is the opinion of the CKD Work Group that this recommendation is appropriate for patients with GFR less than 30 ml/min/1.73 m^2 (CKD Stages 4-5) and less frequent monitoring (eg, every 6 to 12 months) may be acceptable for patients with GFR 30 to 60 mL/min/1.73m^2 (CKD Stage 3) if there is no evidence of malnutrition.

The high prevalence of malnutrition in chronic

Table 83. Serum Albumin and Kidney Function

Author, Year	No. of Subjects	Applicability	GFR Range (mL/min/1.73 m²) 0 30 60 90 120	Results*/ Mean Level	Quality
Kopple,[324] 2000	1,785	†††		⬆	●
Ikizler,[325] 1995	90	†††		⇔	●
Kopple,[338] 1989	89	††		⇔	●
Monteon,[348] 1986	22	††	S_{Cr} = 8.0 ± 2.4 mg/dL	⇔	●
Park,[340] 1997	64	†††		⬆	◎
Ando,[349] 1979	20	††		⇧	◎
Pollock,[341] 1997	439	††		⬆	○
Aparicio,[345] 2000	239	††		3.8 g/dL	●
Stenvinkel,[323] 1999	109	††		3.4 g/dL	●
Stenvinkel,[350] 1998	83	††		3.3 g/dL	●
Walser,[351] 1999	23	†		4.1 g/dL	●
Cupisti,[352] 1990	51	††		3.8 g/dL	◎
Sugimoto,[353] 1991	14	††		3.3 g/dL	◎
Guarnieri,[354] 1986	12	††	S_{Cr} 2.1 ± 0.7 mg/dL	4.3 g/dL	◎
Chauveau,[343] 1999	10	†		4.1 g/dL	◎
Williams,[344] 1991	6	†		3.9 g/dL	◎
Di Landro,[355] 1990	69	††	S_{Cr} 4.3 mg/dL	4.2 g/dL	○
Vetter,[356] 1990	59	†		4.2 g/dL	○

* ⬆ = higher GFR associated with higher serum albumin (statistically significant);
⇧ = higher GFR associated with higher serum albumin;
⇔ = GFR *not* associated with serum albumin.

kidney disease, the association between malnutrition and clinical outcomes, and new evidence that nutrient intake begins to decline at GFR <60 mL/min/1.73 m^2 support the recommendation that nutritional status should be assessed and monitored earlier in the course of chronic kidney disease.

Serum albumin level is lower in patients with decreased GFR (Tables 83 and 84 and Figs 31 and 32) (C, S). Serum albumin is lower at levels of GFR below 60 mL/min/1.73 m^2, indicating a decline in circulating protein levels or serum protein concentrations, protein losses or inflammation.[324,325,338,340,341,348,349] An acceptable goal level for albumin is >4.0 g/dL (bromcresol green method).

Similar findings have been reported for serum total proteins and pre-albumin.

Serum transferrin level is lower in patients with decreased GFR (Table 85 and Fig 33) (C, S). Serum transferrin is lower at lower GFR levels. This is evidenced in patients with chronic

Table 84. Serum Protein & Pre-albumin and Kidney Function

Author, Year	No. of Subjects	Applicability	GFR Range (mL/min/1.73 m²) 0 30 60 90 120	Results*/ Mean Level	Quality
Serum Protein					
Ando,[349] 1979	20			⇧	
Barsotti,[357] 1988	8			6.0 g/dL	
Cupisti,[352] 1990	51			6.7 g/dL	
Williams,[344] 1991	6			6.6 g/dL	
Pre-albumin					
Ikizler,[325] 1995	90			⇧	
Park,[340] 1997	64			⇧	
Chauveau,[343] 1999	10			3.9 g/dL	

* ⇧ = higher GFR associated with higher serum protein or pre-albumin.

kidney disease, with no sign of inflammation, infection, and with stable iron status.[324,325,338,340]

Serum bicarbonate concentration is lower in patients with decreased GFR (Table 86) (C). As GFR falls to <60 mL/min/1.73 m², serum bicarbonate decreases. Low serum bicarbonate is an indicator of acidemia and associated with protein degradation. Low serum bicarbonate has been correlated to low serum albumin.[325,340] See K/DOQI Clinical Practice Guidelines for Nutrition in Chronic Renal Failure, Guideline 14, *Treatment of Low Serum Bicarbonate*:

"Predialysis or stabilized serum bicarbonate levels should be maintained at or above 22 μmol/L."[75]

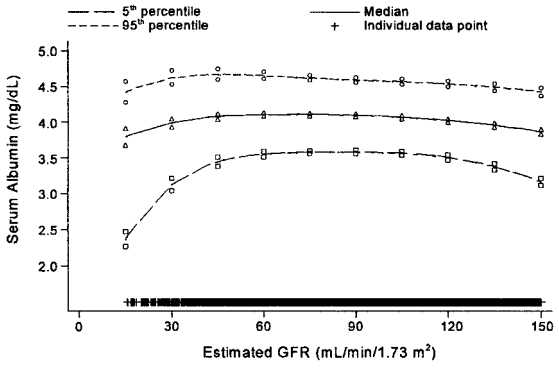


Fig 31. Serum albumin percentiles by GFR adjusted to age. Median and 5th and 95th percentiles of serum albumin among adult participants age 20 years and older in NHANES III, 1988 to 1994. Values are adjusted to age 60 years using a polynomial quantile regression. The estimated GFR for each individual data point is shown with a plus near the abscissa. 95% confidence intervals at selected levels of estimated GFR are demarcated with triangles, squares, and circles.

Serum cholesterol concentration is lower in patients with decreased GFR (Table 87 and Fig 34) (C, S). As GFR decreases to <60 mL/min/1.73 m², serum cholesterol falls, even when controlling for inflammation and comorbid conditions.[324,325,338,339,341]

Body weight, body mass index, percentage body fat, and skin fold thickness are lower in patients with decreased GFR (Tables 88, 89, 90, and 91 and Fig 35) (C, S). As GFR falls to <50 mL/min/1.73 m², measurements of body mass show declines in total mass, fat, and muscle. The correlations may be stronger in men than women. Assessment of body composition, especially with serial measurements can provide valuable information concerning long term adequacy of protein energy nutrition. Changes in body weight, BMI, and body fat in patients with chronic

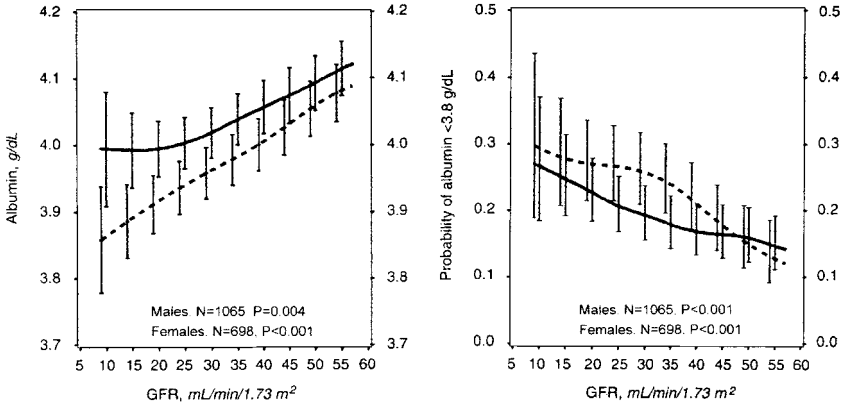


Fig 32. Association of serum albumin and GFR in the MDRD Study. Mean levels of serum albumin and the probability of serum albumin concentrations <3.8 g/dL as a function of GFR (males, solid lines; females, dashed lines). Reprinted with permission.[324]

kidney disease and GFR >60 mL/min/1.73 m^2 have not been assessed.[324,338,341]

LIMITATIONS

There are certain limitations to the information presented herein. The design of most studies measuring nutrition markers in chronic kidney disease is based on data derived from cross-sectional studies. There are very few longitudinal studies available. In addition, there is a lack of uniform collective evaluation of the multiple markers of nutritional status in patients with chronic kidney disease. Although it is known that dietary nutrient intake decreases with GFR, there is only limited evidence that decreased dietary protein intake per se causes poor nutritional status. However, research indicates that when patients receive intensive nutrition therapy and monitoring while the GFR is declining, nutrition status can be maintained.[337,343,345,351,358,365-367]

CLINICAL APPLICATIONS

- Dietary protein prescription in chronic kidney disease is complicated by potential conflict between goals to slow the progression of kidney disease and preserve protein nutri-

Table 85. Transferrin and Kidney Function

Author, Year	No. of Subjects	Applicability	GFR Range (mL/min/1.73 m^2) 0 30 60 90 120	Results*/ Mean Level	Quality
Kopple,[324] 2000	1,785	♦♦♦		⬆	●
Ikizler,[325] 1995	90	♦♦♦		⬆	●
Kopple,[338] 1989	89	♦♦		⇔	●
Park,[340] 1997	64	♦♦♦		⬆	○
Walser,[351] 1999	23	♦		233 mg/dL	●
Cupisti,[352] 1990	51	♦♦		244 mg/dL	○
Guarnieri,[354] 1986	12	♦♦	$S_{0.5}$ 2.1 ± 0.7 mg/dL	223 mg/dL	○
Chauveau,[343] 1999	10	♦		216 mg/dL	○
Vetter,[356] 1990	59	♦		210 mg/dL	○

* ⬆ = higher GFR associated with higher transferrin (statistically significant);
⇔ = GFR level *not* associated with transferrin.

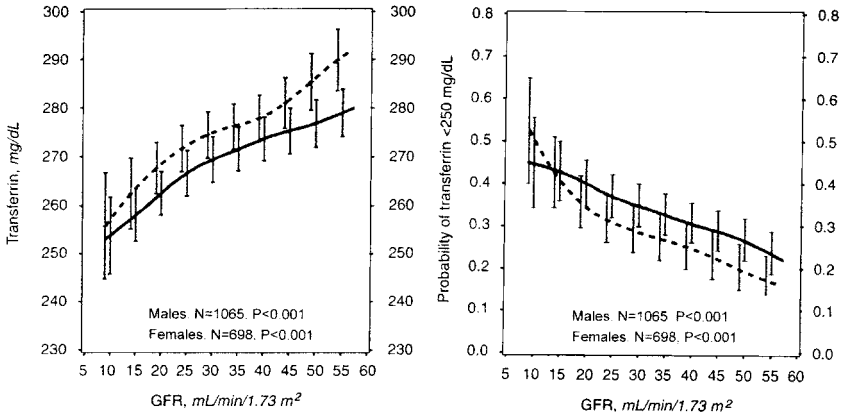


Fig 33. Association of serum transferrin and GFR in the MDRD Study. Mean levels of serum transferrin and the probability of serum transferrin concentrations <250 mg/dL as a function of GFR (males, solid lines; females, dashed lines). Reprinted with permission.[324]

tional status. There is insufficient evidence to recommend for or against routine prescription of dietary protein restriction to slow progression (see Guideline 13). Thus, the RDA for protein of 0.75 g/kg/d appears reasonable in patients with GFR >30 mL/min/1.73 m^2 (CKD Stages 1–3). A lower protein intake of 0.6 g/kg/d can be considered for patients with lower GFR (Stages 4 and 5) to slow progression and minimize accumulation of uremic toxins. Individual decision-making is recommended after discussion of risks and benefits.

- Maintaining adequate energy intake is essential at all stages of chronic kidney disease.
- Assessment of nutritional status in chronic kidney disease requires multiple markers to assess protein status, fat stores, body composition, and dietary protein and energy intake.
- The nutritional status of patients with chronic kidney disease should be monitored at regular intervals: every 1 to 3 months for patients with GFR <30 mL/min/1.73 m^2 (CKD Stages 4 and 5) and every 6 to 12 months for patients with GFR 30 to 59 mL/min/1.73 m^2 (CKD Stage 3).
- The extent of PEM can be considered as an indication for the initiation of kidney replacement therapy. If PEM develops or persists despite vigorous attempts to optimize protein and energy intake, and there is no apparent cause for malnutrition other than

Table 86. Serum Bicarbonate and Kidney Function

Author, Year	No. of Subjects	Applicability	GFR Range (mL/min/1.73 m^2) 0 30 60 90 120	Results*/ Mean Level	Quality
Ikizler,[325] 1995	90	♟♟♟		↑	●
Park,[340] 1997	64	♟♟♟		↑	○
Aparicio,[345] 2000	239	♟♟		HCO_3^- = 23 mEq/L	●
Walser,[351] 1999	23	♟		HCO_3^- = 21 mEq/L	●
Mazouz,[347] 1999	49	♟♟		HCO_3^- = 24 mEq/L	○
Jenkins,[358] 1989	11	♟♟		HCO_3^- = 19 mEq/L	○
Williams,[344] 1991	6	♟		HCO_3^- = 17 mEq/L	○

* ↑ = higher GFR associated with higher serum bicarbonate (statistically significant).

Table 87. Lipids and Kidney Function

Author, Year	No. of Subjects	Applicability	GFR Range (mL/min/1.73 m^2) 0 30 60 90 120	Results*/ Mean Level**	Quality
Total Cholesterol					
Kopple,[324] 2000	1,785			⬆ (men) ⇧ (women)	●
Ikizler,[325] 1995	90			⬆	●
Kopple,[338] 1989	89			⇔	●
Coggins,[339] 1994	33			⇔	●
Pollock,[341] 1997	439			⇔	○
Triglycerides					
Pollock,[341] 1997	439			⬆	○
LDL or HDL					
Coggins,[339] 1994	33			⇩ (LDL)	●
Coggins,[339] 1994	33			⇧ (HDL)	●
Total Cholesterol					
Stenvinkel,[350] 1998	83			230 mg/dL	●
Huang,[359] 1998	83			210 mg/dL	●
Zeller,[360] 1991	35			200 mg/dL	●
Walser,[351] 1999	23			204 mg/dL	●
Mazouz,[347] 1999	49			240 mg/dL	◎
Guarnieri,[354] 1986	12		S_{Cr} 2.1 ±0.7 mg/dL	196 mg/dL	◎
Jenkins,[358] 1989	11			210 mg/dL	◎
Williams,[344] 1991	6			290 mg/dL	◎
Di Landro,[355] 1990	69		S_{Cr} 4.3 mg/dL	235 mg/dL	○
D'Amico,[361] 1990	108		S_{Cr} 3.3 ±1.9 mg/dL	217 mg/dL	○

low nutrient intake, initiation of maintenance dialysis or kidney transplant is recommended. See CKD Guideline 1, p. S46. In general, this guideline applies to patients with GFR <15 mL/min/1.73 m^2 (CKD Stage 5) but may apply to some patients with higher GFR levels.

IMPLEMENTATION ISSUES

In the United States, implementation of the medical nutrition therapy law for reimbursement through Medicare will allow for the provision of nutrition monitoring as described in these guidelines. Studies show that the most effective nutrition interventions in patients with chronic

Table 87. Lipids and Kidney Function (cont.)

Author, Year	No. of Subjects	Applicability	GFR Range (mL/min/1.73 m²) 0 30 60 90 120	Results/ Mean Level*	Quality
Triglycerides					
Stenvinkel,[350] 1998	83	♦♦		210 mg/dL	●
Huang,[359] 1998	83	♦♦		174 mg/dL	●
Zeller,[360] 1991	35	♦♦		162 mg/dL	●
Walser,[351] 1999	23	♦		158 mg/dL	●
Mazouz,[347] 1999	49	♦♦		180 mg/dL	◉
Guarnieri,[354] 1986	12	♦♦	S_{Cr} 2.1 ±0.7 mg/dL	115 mg/dL	◉
Jenkins,[358] 1989	11	♦♦		220 mg/dL	◉
Williams,[344] 1991	6	♦		260 mg/dL	◉
D'Amico,[361] 1990	108	♦	S_{Cr} 3.3 ±1.9 mg/dL	158 mg/dL	○
Di Landro,[355] 1990	69	♦♦	S_{Cr} 4.3 mg/dL	182 mg/dL	○
Miscellaneous					
D'Amico,[361] 1990	108	♦	S_{Cr} 3.3 ±1.9 mg/dL	43 mg/dL (HDL)	○
Zeller,[360] 1991	35	♦♦		2.9 (LDL:HDL ratio)	●

* ⬆ = higher GFR associated with higher level of indicated lipid (statistically significant);
⇧ = higher GFR associated with higher level of indicated lipid;
⇔ = GFR level *not* associated with level of indicated lipid;
⇩ = higher GFR associated with lower level of indicated lipid.

** Units conversion: to convert from mg/dL to mmo/L for cholesterol (total, LDL and HDL) multiply by 0.02586; for triglycerides multiply by 0.01129.

Abbreviations: HDL, high density lipoprotein; LDL, low density lipoprotein

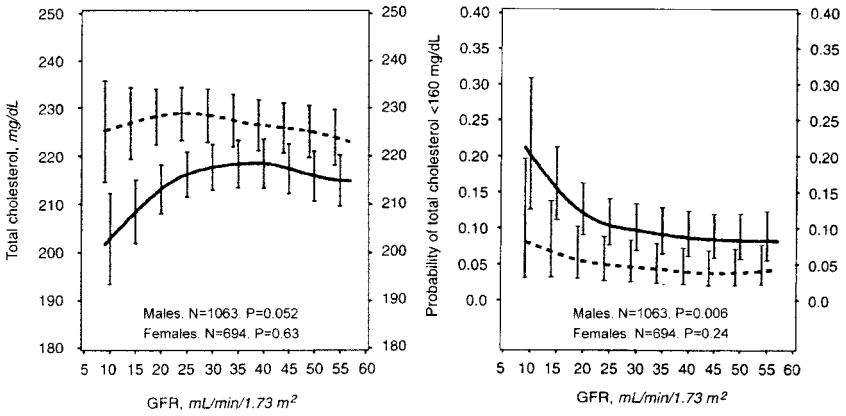


Fig 34. Association of serum cholesterol and GFR in the MDRD Study. Mean levels of serum cholesterol and the probability of serum cholesterol concentrations <160 mg/dL as a function of GFR (males, solid lines; females, dashed lines). Reprinted with permission.[324]

Table 88. Body Mass Index and Kidney Function

Author, Year	No. of Subjects	Applicability	GFR Range (mL/min/1.73 m²) 0 30 60 90 120	Results*/ Mean Level	Quality
Kopple,[324] 2000	1,785	♦♦♦		⬆ (men) ⇔ (women)	●
Kopple,[338] 1989	89	♦♦		⇔	●
Pollock,[341] 1997	439	♦♦		⬆	○
Aparicio,[345] 2000	239	♦♦		22.3 kg/m²	●
Stenvinkel,[323] 1999	109	♦♦		24.4 kg/m²	●
Stenvinkel,[350] 1998	83	♦♦		24.6 kg/m²	●
Huang,[359] 1998	83	♦♦		30.6 kg/m²	●
Guarnieri,[354] 1986	12	♦♦	S_{Cr} 2.1 ± 0.7 mg/dL	24.0 kg/m²	◎
Chauveau,[343] 1999	10	♦		24.6 kg/m²	◎
Parillo,[362] 1988	6	♦	S_{Cr} = 3.8 ± 1.9 mg/dL	27.6 kg/m²	◎

* ⬆ = higher GFR associated with higher body mass index (statistically significant);
⇔ = GFR *not* associated with body mass index.

Table 89. Ideal or Standard Body Weight and Kidney Function

Author, Year	No. of Subjects	Applicability	GFR Range (mL/min/1.73 m²) 0 30 60 90 120	Results*/ Mean Level	Quality
Kopple,[324] 2000	1,785	♦♦♦		⬆ (men) ⇔ (women)	●
Kopple,[338] 1989	89	♦♦		⬆ (men) ⇔ (women)	●
Goodship,[363] 1990	10	♦		110%	●
D'Amico,[361] 1990	108	♦	S_{Cr} 3.3 ±1.9 mg/dL	110%	○

* ⬆ = higher GFR associated with higher body weight (statistically significant);
⇔ = GFR *not* associated with body weight.

kidney disease involve patient training in self management skills and frequent, ongoing feedback, and interventions with the nutrition team.[368-371] Medical nutrition therapy for patients with chronic kidney disease must therefore include adequate time for nutrition assessment and education and regular, scheduled nutrition appointments.

Although occasionally a care provider, or other individual, may possess the expertise and time to conduct nutritional assessment, use dietary interviews and records to assess protein energy intake, assess body muscle and fat stores, interpret biochemical markers of nutrition status and relate to dietary intake, and provide nutritional therapy (develop a plan for nutritional management, counsel the patient and family on appropriate dietary protein energy intake, monitor nutrition intake, and provide encouragement to maximize dietary adherence)—a registered dietitian, trained and experienced in CKD nutrition, is best qualified to carry out these tasks. Such an individual not only has undergone all of the training required to become a

Table 90. Body Tissue Composition (Muscle) and Kidney Function

Author, Year	Measurement	No. of Subjects	Applicability	GFR Range (mL/min/1.73 m²) 0 30 60 90 120	Results*/ Mean Level	Quality
Kopple,[324] 2000	Arm muscle area	1,785	♀♀♀		⬆ (men) ⇔ (women)	●
Kopple,[338] 1989	Arm muscle area	89	♀♀		⬆ (men) ⇔ (women)	●
Guarnieri,[354] 1986	Arm muscle area	12	♀♀	S_{Cr} 2.1 ±0.7 mg/dL	4,861 mm²	○
Guarnieri,[354] 1986	Arm muscle circumference	12	♀♀	S_{Cr} 2.1 ±0.7 mg/dL	24.6 cm	○
Chauveau,[343] 1999	Arm muscle circumference	10	♀		30.9 cm	○
Williams,[344] 1991	Arm muscle circumference	6	♀		28.5 cm	○
Cupisti,[352] 1990	Arm muscle circumference	51	♀♀		23.7 cm (men) 21.8 cm (women)	○
Jenkins,[358] 1989	Arm muscle circumference	11	♀♀		25.2 cm	○

Bold horizontal line divides studies by type of measurement (arm muscle area vs. arm muscle circumference).

* ⬆ = higher GFR associated with greater muscle mass (statistically significant);
⇔ = GFR *not* associated with muscle mass.

Table 91. Body Tissue Composition (Fat) and Kidney Function

Author, Year	Measurement	No. of Subjects	Applicability	GFR Range (mL/min/1.73 m²) 0 30 60 90 120	Results*/ Mean Level	Quality
Kopple,[324] 2000	Triceps skinfold thickness	1,785	♀♀♀		⬆	●
Kopple,[338] 1989	Triceps skinfold thickness	89	♀♀		⇔	●
Kopple,[324] 2000	Biceps skinfold thickness	1,785	♀♀♀		⬆	●
Monteon,[348] 1986	% Body fat	22	♀♀	S_{Cr} 8.0 ±2.4 mg/dL	⬆	●
Cupisti,[352] 1990	Triceps skinfold thickness	51	♀♀		11 mm (men) 16 mm (women)	○
Guarnieri,[354] 1986	Triceps skinfold thickness	12	♀♀	S_{Cr} 2.1 ±0.7 mg/dL	13.2 mm	○
Chauveau,[343] 1999	Triceps skinfold thickness	10	♀		14.5 mm	○
Williams,[344] 1991	Triceps skinfold thickness	6	♀		17.2 mm	○
Guarnieri,[354] 1986	Arm fat area	12	♀♀	S_{Cr} 2.1 ±0.7 mg/dL	1,792 mm²	○
Woodrow,[364] 1996	Total body fat	23	♀	S_{Cr} > 5.6 mg/dL	22%–25%	○

Bold horizontal lines divide studies by type of measurement used.

* ⬆ = higher GFR associated with greater body fat (statistically significant);
⇔ = GFR *not* associated with body fat.

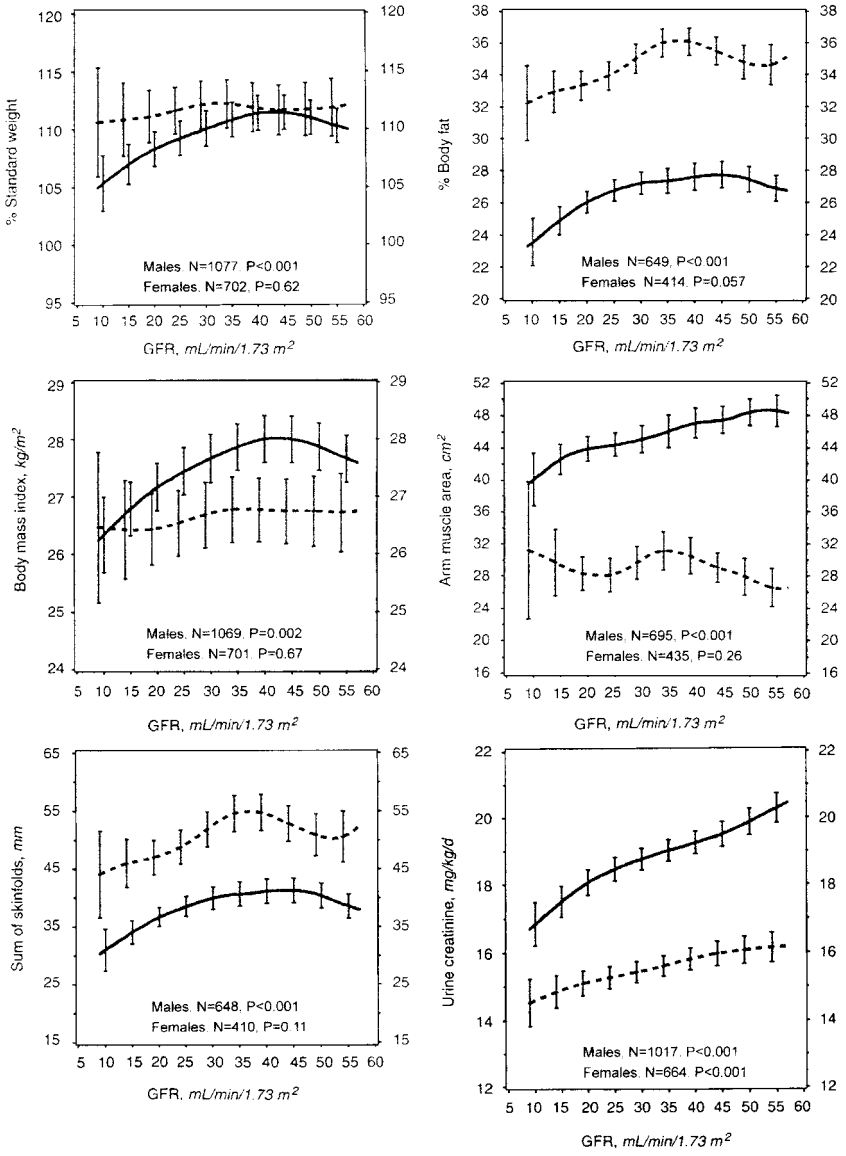


Fig 35. Association of body composition and GFR in the MDRD Study. Mean levels of anthropometric measures of nutritional status as a function of GFR (males, solid lines; females, dashed lines). Reprinted with permission.[324]

registered dietitian, including in many instances a dietetic internship, but has also received formal or informal training in CKD nutrition. Such a person is particularly experienced in working with patients with chronic kidney disease and the nephrology team (see K/DOQI Clinical Practice Guidelines for Nutrition in Chronic Renal Failure, Appendix IV, *Role of the Renal Dietitian*[75]).

Research Recommendations

Although the data presented herein is compelling, more research, especially prospective studies evaluating the impact of kidney disease on nutritional parameters, is needed. Importantly, studies to define the optimal methods to evaluate nutritional status in chronic kidney disease patients are critical. Prospective studies evaluating the impact of different levels of nutritional status on subsequent outcome in chronic kidney disease patients should also be performed. Finally, prospective studies evaluating the impact of intensive nutritional counseling on nutritional status and possibly clinical outcome in chronic kidney disease patients should be carried out.

GUIDELINE 10. ASSOCIATION OF LEVEL OF GFR WITH BONE DISEASE AND DISORDERS OF CALCIUM AND PHOSPHORUS METABOLISM

Bone disease and disorders of calcium and phosphorus metabolism develop during the course of chronic kidney disease and are associated with adverse outcomes.

- **Patients with GFR <60 mL/min/1.73 m^2 should be evaluated for bone disease and disorders of calcium and phosphorus metabolism.**
- **Patients with bone disease and disorders of bone metabolism should be evaluated and treated—see forthcoming K/DOQI Clinical Practice Guidelines on Bone Metabolism and Disease in Chronic Kidney Disease**.

BACKGROUND

Chronic kidney disease is associated with a variety of bone disorders and disorders of calcium and phosphorus metabolism. The major disorders of bone can be classified into those associated with high parathyroid hormone (PTH) levels (osteitis fibrosa cystica) and those with low or normal PTH levels (adynamic bone disease). The hallmark lesion of chronic kidney disease is osteitis fibrosa, due to secondary hyperparathyroidism. However, with the advent of intensive treatments for secondary hyperparathyroidism, the prevalence of disorders associated with low or normal PTH levels has increased.

Irrespective of the cause, bone disease can lead to pain and an increased incidence of fractures. Abnormal calcium-phosphorus metabolism and hyperparathyroidism can also lead to calcification of blood vessels and potentially an increased risk of cardiovascular events.

The stage of chronic kidney disease at which bone disease begins to develop has not been well documented, nor has a consensus been developed regarding the best screening measures for detecting early abnormalities of calcium-phosphorus metabolism and bone disease. The aim of this guideline is to provide evidence on the association of level of GFR with disorders of calcium-phosphorus metabolism and bone disease and to provide recommendations on how to approach this complication of chronic kidney disease.

RATIONALE

Bone Disease in Chronic Kidney Disease

Bone disease associated with chronic kidney disease is composed of a number of abnormalities of bone mineralization. The major disorders can be classified into those associated with high bone turnover and high PTH levels (including osteitis fibrosa, the hallmark lesion of secondary hyperparathyroidism, and mixed lesion) and low bone turnover and low or normal PTH levels (osteomalacia and adynamic bone disease).[372] Osteomalacia may be related to vitamin D deficiency, excess aluminum, or metabolic acidosis; whereas adynamic bone disease may be related to over-suppression of PTH with calcitriol.[372-374]

The pathophysiology of bone disease due to secondary hyperparathyroidism is related to abnormal mineral metabolism: (1) decreased kidney function leads to reduced phosphorus excretion and consequent phosphorus retention; (2) elevated serum phosphorus can directly suppress calcitriol (dihydroxyvitamin D_3) production; (3) reduced kidney mass leads to decreased calcitriol production; (4) decreased calcitriol production with consequent reduced calcium absorption from the gastrointestinal tract contributes to hypocalcemia, as does abnormal calcium-phosphorus balance leading to an elevated calcium-phosphorus product.[375,376] Hypocalcemia, reduced calcitriol synthesis, and elevated serum phosphorus levels stimulate the production of PTH and the proliferation of parathyroid cells,[377-379] resulting in secondary hyperparathyroidism. High PTH levels stimulate osteoblasts and result in high bone turnover. The hallmark lesion of secondary hyperparathyroidism is osteitis fibrosa cystica. High bone turnover leads to irregularly woven abnormal osteoid, fibrosis, and cyst formation, which result in decreased cortical bone and bone strength and an increased risk of fracture.

Low turnover bone disease has two subgroups, osteomalacia and adynamic bone dis-

ease. Both lesions are characterized by a decrease in bone turnover or remodeling, with a reduced number of osteoclasts and osteoblasts, and decreased osteoblastic activity. In osteomalacia there is an accumulation of unmineralized bone matrix, or increased osteoid volume, which may be caused by vitamin D deficiency or excess aluminum. Adynamic bone disease is characterized by reduced bone volume and mineralization and may be due to excess aluminum or oversuppression of PTH production with calcitriol.[372]

Other Complications of Abnormal Calcium-Phosphorus Metabolism

In addition to abnormalities in bone metabolism, abnormal calcium-phosphorus metabolism may lead to calciphylaxis or extraosseous calcification of soft tissue and vascular tissue. This complication in its full manifestation has been reported to affect approximately 1% of dialysis patients.[380] However, in studies of coronary artery calcification using electron beam computed tomography, dialysis patients had coronary calcification scores that were several-fold higher than those of patients with known coronary artery disease.[381] The pathogenesis remains unclear, but hyperphosphatemia, hypercalcemia, elevated calcium-phosphorus product, and increased PTH levels are probable contributors.

Markers of Bone Disease and Abnormal Calcium-Phosphorus Metabolism in Chronic Kidney Disease

Bone biopsy following double-tetracycline labeling is the gold standard for the diagnosis of bone disease in chronic kidney disease and is the only means of definitively differentiating them. Five bone lesions associated with chronic kidney disease have been classified based on bone formation rate, osteoid area, and fibrosis on bone biopsy of patients with kidney failure[372,382] (Table 92).

Bone biopsy is not easy, nor necessary in routine clinical practice. Classically, bone resorption can be seen on plain radiographs in cases of advanced osteitis fibrosa, but radiological studies, including densitometry, have not been conclusively shown to differentiate the various types of bone disease associated with kidney failure. Bone biopsy is currently recommended only for patients with symptomatic disease in whom interventions are being contemplated (such as parathyroidectomy or desferoxamine treatment for elevated aluminum levels)[383] or for research of the effectiveness of therapies or alternative diagnostic tests.[384] In the absence of direct pathologic studies, clinicians have relied on biochemical data to determine the probable presence of, or assess the risk for, bone abnormalities. Low calcitriol (dihydroxyvitamin D_3) and calcium levels, and high phosphorus and PTH levels, are the classic abnormalities which develop with decreased GFR.[385] The biochemical studies in common use are serum phosphorus, calcium, and PTH levels. Calcitriol levels can also be measured, but this is not commonly done in clinical practice. Serum phosphorus and calcium levels are used in screening for abnormalities of mineral metabolism that may lead to PTH excess; however, PTH levels may begin to rise even before there is appreciable hyperphosphatemia.[379] Hence, the recommendation to obtain PTH levels in the assessment of bone disease in chronic kidney disease.

Table 92. Histologic Classification of Bone Lesions Associated with Kidney Disease

Lesions	Bone Formation Rate ($\mu m^2/mm^2$ tissue area/day)	Osteoid Area (%)	Fibrosis (%)
Aplastic (adynamic):	<108	<15%	<0.5%
Osteomalacia:	<108	>15%	<0.5%
Mild:	>108	<15%	<0.5%
Osteitis Fibrosa:	>108	<15%	>0.5%
Mixed:	>108	>15%	>0.5%

An ideal serologic marker would be unique to bone and would be well correlated to histologic findings on biopsy. Two markers studied more extensively include PTH and bone alkaline phosphatase (bAP). PTH secretion is directly correlated with bone turnover, but PTH levels are not reliably correlated with bone turnover among dialysis patients, especially in the middle ranges.[386,387] PTH levels $<$65 pg/mL were found to be predictive of normal bone or low turnover lesions, and PTH levels $>$450 pg/mL were predictive of high turnover lesions, but levels in between did not have good predictive value. Overall bone turnover could not be predicted in 30% of HD and 50% of PD patients.[387] In another study, low turnover lesions were noted in

the majority of patients with PTH levels <100 pg/mL and high turnover lesions in the majority of patients with PTH levels >200 to 300 pg/mL.[386] High bAP levels have been associated with high bone turnover and low levels with adynamic bone disease in dialysis patients. In one study, the combination of high bone alkaline phosphatase levels with high PTH levels increased the sensitivity of diagnosis of high turnover lesions; conversely, low levels of both of these markers result in increased sensitivity for diagnosis of low turnover lesions. However, specific cut-off levels for bAP have varied in the few studies examining the relationship to bone histology.[383]

Other markers of bone disease not yet fully investigated nor in widespread clinical use include osteocalcin, β2 microglobulin, procollagen type I carboxy-terminal propeptides (PICP), and type I collagen cross linked telopeptides (ICTP), among others. PICP has been correlated with bone formation, and ICTP and osteocalcin been correlated with bone resorption. However, levels of many of these markers are affected by age, diet, liver function, and kidney function; thus, interpretation of levels is difficult.[383]

Thus, abnormalities of bone mineral metabolism are present if there is an elevated serum phosphorus or PTH level or reduced serum calcium or calcitriol level. Given the possibility of an elevated PTH level in the face of normal serum calcium and phosphorus levels, the diagnosis of early abnormality of mineral metabolism requires measurement of PTH levels. Extreme elevations of serum PTH levels are more convincingly associated with high turnover lesions than low levels with low turnover lesions. Definitive diagnosis of type of bone disease requires bone biopsy.

Strength of Evidence

Bone disease and disorders of calcium and phosphorus metabolism develop during the course of chronic kidney disease (R). Radiologic and histologic changes of bone disease can be demonstrated in about 40% and nearly 100%, respectively, of patients with severely decreased kidney function and kidney failure.[388,389] However, the abnormalities that lead to bone disease begin to occur at earlier stages of chronic kidney disease. Elevated levels of PTH and phosphorus, reduced levels of calcium, and reduced urinary phosphate excretion have been described among patients with GFR <70 mL/min or lower.[372,379,386,390,391] Histologic changes have also been shown to occur at earlier stages of chronic kidney disease. In a study of 176 patients with creatine clearances of 15 to 50 mL/min, 75% had "important histological abnormalities, with the majority having osteitis fibrosa with or without osteomalacia."[392] In another study of patients with creatinine clearances of 20 to 59 mL/min, 87% of patients had abnormal bone histology, and the majority had lesions of high bone formation rate associated with hyperparathyroidism.[374]

Bone disease and disorders of bone metabolism are associated with worse outcomes in chronic kidney disease (R). The consequences of abnormal bone mineral metabolism have been studied primarily in patients without kidney disease and in patients with kidney failure.[393,394] Hyperparathyroidism has been associated with abnormal bone histology, bone pain, and fractures among patients with either primary and secondary hyperparathyroidism,[395-397] and low PTH levels have been more recently recognized to result in an increased risk of vertebral and pelvic fractures.[398,399]

Calcification of cardiac muscle and coronary vasculature may lead to arrhythmia, left ventricular dysfunction, ischemia, congestive heart failure, and death. Calciphylaxis results in skin lesions that may become infected or gangrenous, leading to significant morbidity and mortality among patients on dialysis.[380,394,400] Elevated phosphorus and calcium-phosphorus product has also been linked to increased mortality among patients on dialysis.[400,401] It has been hypothesized that elevated phosphorus levels may hasten the loss of kidney function, possibly via calcium-phosphorus precipitation.[402]

In addition, there is some experimental evidence that elevated PTH levels may be associated with myocardial dysfunction, and impaired skeletal muscle, neurological, and hematopoietic function.[393] The impact of PTH levels on mortality appears conflicting. One study of dialysis patients reported an increased risk of death among dialysis patients with low serum PTH levels,[400,403] while another study of patients in an

Table 93. Parathyroid Hormone and Kidney Function

Author, Year	No. of Subjects	Applicability	GFR Range (mL/min/1.73 m^2) 0 30 60 90 120	Results*	Quality
Martinez,[405] 1997	157	†††		↓	●
Pitts,[406] 1988	72	†††		↓	●
St. John,[407] 1992	51	†††		↓	●
Reichel,[408] 1991	85	††		↓	●
von Lilienfeld-Toal,[409] 1982	81	††		↓	●
Cheung,[410] 1983	39	†††	S_{Cr} 3.4 ±0.3 mg/dL	↓	○
Fajtova,[411] 1995	39	†††		↓	○
Rix,[412] 1999	202	††		↓	○
Yumita,[413] 1996	195	††	S_{Cr} <1–>8 mg/dL	↓	○
Christensen,[414] 1977	188	††		↓	○
Kates,[378] 1997	84	††		↓	○
Malluche,[415] 1976	72	††		↓	○
McGonigle,[416] 1984	60	††	S_{Cr}: 5–11.5 mg/dL	↓	○
Saha,[417] 1994	50	††		↓	○
Messa,[418] 1995	43	††		↓	○
Tessitore,[419] 1987	41	††		⇩	○
Coen,[420] 1989	32	††	S_{Cr} 6.5 ±2.9 mg/dL	↓	○
Tougaard,[421] 1977	24	††		↓	○
Madsen,[422] 1976	15	††		⇩	○
Bedani,[423] 1985	61	††		↓	○
Arata,[424] 1976	31	††		⇩	○
Arnaud,[425] 1973	~124[a]	†		⇩	○
Reiss,[426] 1968	6	†		⇩	○

* ↓ = higher GFR associated with lower parathyroid hormone (statistically significant);
⇩ = higher GFR associated with lower parathyroid hormone.

[a] No data given on exact number of subjects; 124 points counted on graph; no information on whether data-points each represent individual subjects.

Table 94. Fractional Excretion of Phosphorus and Kidney Function

Author, Year	No. of Subjects	Applicability	GFR Range (mL/min/1.73 m^2) 0 30 60 90 120	Results*	Quality
Pitts,[406] 1988	72	🧍🧍🧍		⬇	●
Massry,[427] 1973	105	🧍🧍		⇩	◎
Slatopolsky,[428] 1968	30	🧍🧍		⬇	○

* ⬇ = higher GFR associated with lower fractional excretion of phosphate (statistically significant);
⇩ = higher GFR associated with lower fractional excretion of phosphate.

emergency room reported an increased risk of death among patients with high PTH levels.[404]

Onset and severity of bone disease and abnormalities of bone mineral metabolism are related to the level of GFR; below a GFR of approximately 60 mL/min/1.73 m^2, there is a higher prevalence of abnormalities of bone metabolism (C, S).

PTH levels are elevated in patients with decreased GFR and likely are the earliest marker of abnormal bone mineral metabolism (Tables 93 and 94 and Figs 36, 37, and 38) (C, S). The studies relating PTH levels to kidney function date back to the 1960s, with sample sizes ranging from 6 to over 200 subjects with kidney disease. Each of the 23 studies on this topic reviewed for this guideline consistently demonstrated the expected relationship of increasing serum PTH levels with decreasing levels of kidney function. Further details of these studies are presented in Table 93. Because of the variety of assays used to measure PTH and methods used to estimate level of kidney function, no attempt was made to combine data from different studies. However, it is evident and currently accepted that the intact PTH test provides the most consistently reliable measure of PTH levels.

There were four separate studies that examined the threshold creatinine clearance or GFR levels at which PTH levels begin to rise; these threshold levels ranged from <70 mL/min to <40 mL/min.[406,411,415,425] In addition, analyses of data from a single study[288] demonstrate an inverse correlation between level of GFR and PTH

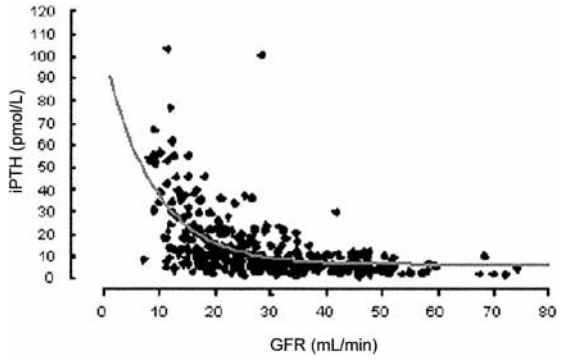


Fig 36. Scatterplot of iPTH versus GFR. These data are based on the results of 446 patients enrolled in the Canadian Multicentre Longitudinal Cohort study of patients with chronic kidney disease. All patients were referred to nephrologists between 1994 and 1997. No patient was receiving erythropoiten therapy at the time of enrollment, and no patient had an AV fistula. Intact molecule PTH assay is reported in pica moles per liter, and GFR is calculated using the modified MDRD formula (using age, race, gender, and serum creatinine). Adapted and reprinted with permission.[288]

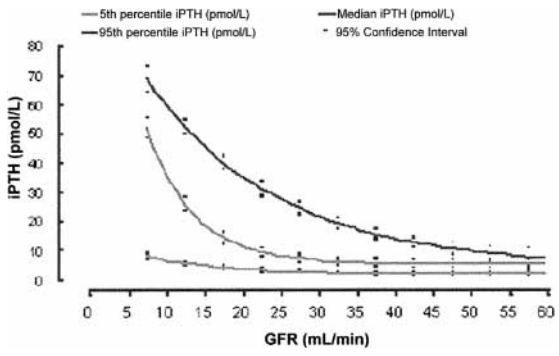


Fig 37. iPTH percentiles by GFR. These data are based on the results of 446 patients enrolled in the Canadian Multicentre Longitudinal Cohort study of patients with chronic kidney disease. All patients were referred to nephrologists between 1994 and 1997. No patient was receiving erythropoiten therapy at the time of enrollment, and no patient had an AV fistula. Intact molecule PTH assay is reported in pica moles per liter, and GFR is calculated using the modified MDRD formula (using age, race, gender, and serum creatinine). Data are presented as median iPTH and 5th and 95th percentiles. Adapted and reprinted with permission.[288]

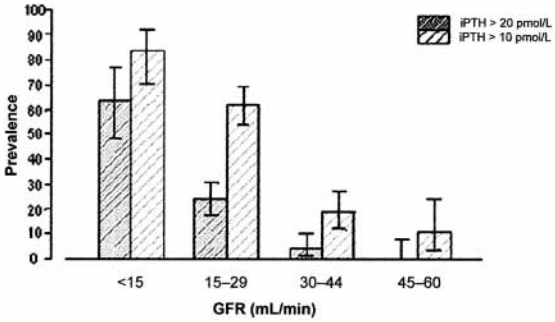


Fig 38. Prevalence of high iPTH by GFR category. These data are based on the results of 446 patients enrolled in the Canadian Multicentre Longitudinal Cohort study of patients with chronic kidney disease. All patients were referred to nephrologists between 1994 and 1997. No patient was receiving erythropoietin therapy at the time of enrollment, and no patient had an AV fistula. Intact molecule PTH assay is reported in pico moles per liter, and GFR is calculated using the modified MDRD formula (using age, race, gender, and serum creatinine). Adapted and reprinted with permission.[288]

(Figs 36 and 37) and an increasing prevalence of abnormally elevated PTH levels with decreasing GFR (Fig 38). Therefore, the preponderance of data support that serum PTH levels are increased in patients with decreased GFR.

Consistent with these observations, fractional excretion of phosphorous is higher at lower GFRs (Table 94).

Serum calcium levels are frequently, but not consistently, abnormal with decreased GFR (Table 95 and Figs 39 and 40) (C, S). The studies relating serum total or ionized calcium levels to kidney function date back to the 1960s, with sample sizes ranging from 15 to over 125 subjects with kidney disease. The studies were conflicting in that about one third (7/20) did not demonstrate the expected relationship between serum calcium levels and kidney function, that is, they did not show lower serum calcium levels among patients with worse kidney function. The remaining studies (13/20) showed that serum calcium levels were lower with lower levels of kidney function.

These data do not consistently show that there is a decrease in calcium levels with declining kidney function. This was not as expected based on the "known" pathophysiology of bone mineral metabolism. The studies showing conflicting results are of similar methodological quality and sample size. In summary, there is not a clear relationship of the level of serum calcium to the level of kidney function over a wide range of kidney function in the reviewed studies.

Similarly, analysis of data from NHANES III does not demonstrate a convincing relationship between serum calcium levels (adjusted for albumin) and level of GFR, although few patients had GFR below 30 ml/min/1.73 m^2 (Fig 39).

However, analyses of data from a single study with a large number of individuals with decreased GFR[288] demonstrate lower serum calcium levels and higher prevalence of lower serum calcium levels among individuals with lower GFR, in particular below a GFR of $<$ 30 mL/min/1.73 m^2 (Fig 40).

The combination of the available information regarding pathophysiology of bone disease in chronic kidney disease and the available evidence reviewed herein would suggest that serum calcium levels are affected by the level of kidney function, though abnormalities in serum calcium levels may not become evident until GFR is $<$30 mL/min/1.73 m^2.

Serum phosphorus levels are elevated in patients with decreased GFR (Table 96 and Figs 41, 42, and 43) (C, S). There were 21 studies relating serum phosphorus levels to kidney function reviewed for this guideline. The sample sizes ranged from 15 to over 250 subjects with kidney disease. Fifteen studies showed the expected association of higher serum phosphorus levels with lower kidney function. The remaining 6 studies did not show an association of kidney function with serum phosphorus levels, although one did find a trend for increasing phosphorus levels when creatinine clearance was below 50 mL/min.[405] There were four studies that provided sufficient information to determine a threshold level of kidney function at which phosphorus levels start to rise. The apparent threshold GFR ranged from 20 to 50 mL/min/1.73 m^2.

In addition, analyses of data from a single study[288] and from an analysis of data from NHANES III, demonstrate an increase in serum phosphorus levels (Fig 41) and an increasing prevalence of abnormally elevated serum phosphorus (Fig 42), with lower GFR. Concomitantly, NHANES III data showed that

Table 95. Serum Calcium and Kidney Function

Author, Year	No. of Subjects	Applicability	GFR Range (mL/min/1.73 m²) 0 30 60 90 120	Results*	Quality
Martinez,[405] 1997	157	†††		⇔	●
Pitts,[406] 1988	72	†††		⇑	●
St. John,[407] 1992	51	†††		⇑	●
Reichel,[408] 1991	85	††		⇔	●
von Lilienfeld-Toal,[409] 1982	81	††		⇑	●
Cheung,[410] 1983	39	†††	S_{Cr} 3.4 ±0.3 mg/dL	⇔	○
Fajtova,[411] 1995	39	†††		⇑	○
Coburn,[429] 1973	256	††	S_{Cr} 11.1 ±7.6 mg/dL	⇧	○
Rix,[412] 1999	202	††		⇑	○
Yumita,[413] 1996	195	††	S_{Cr} <1–>8 mg/dL	⇔	○
Christensen,[414] 1977	188	††		⇑	○
Coburn,[430] 1969	126	††		⇧	○
Massry,[427] 1973	105	††		⇧	○
Kates,[378] 1997	84	††		⇑	○
Saha,[417] 1994	50	††		⇔	○
Messa,[418] 1995	43	††		⇔	○
Coen,[420] 1989	32	††	S_{Cr} 6.5 ±2.9 mg/dL	⇑	○
Tougaard,[421] 1977	24	††		⇑	○
Madsen,[422] 1976	15	††		⇔	○
Arata,[424] 1976	31	††		⇧	○

* ⇑ = higher GFR associated with higher serum calcium (statistically significant);
⇧ = higher GFR associated with higher serum calcium;
⇔ = GFR *not* associated with serum calcium.

calcium-phosphorus product and prevalence of elevated calcium phosphorus product were higher in individuals with lower GFR (Fig 43).

Overall, these data confirm that serum phosphorus level is higher in individuals with decreased kidney function and suggest that serum phosphorus levels become abnormal in some patients at GFR below approximately 60 mL/min/1.73 m^2.

Vitamin D_3 levels are decreased among patients with decreased GFR (Table 97) (C). There were 14 studies relating vitamin D_3 (calcitriol) levels to kidney function reviewed for this guideline, with sample sizes ranging from 39 to

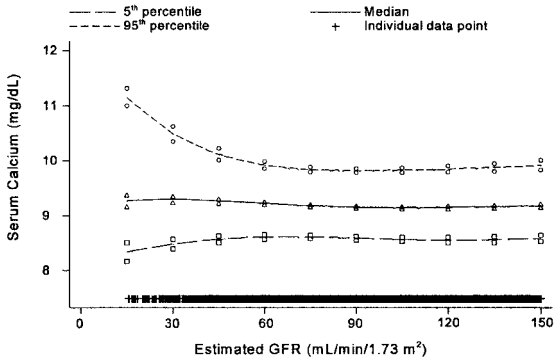


Fig 39. Serum calcium levels (adjusted for albumin) versus GFR. Median and 5th and 95th percentiles of serum calcium, adjusted for serum albumin, among adult participants age 20 years and older in NHANES III, 1988 to 1994. Values are adjusted to age 60 years using a polynomial quantile regression. The estimated GFR for each individual data point is shown with a plus near the abscissa. 95% confidence intervals at selected levels of estimated GFR are demarcated with triangles, squares, and circles.

over 200 subjects with kidney disease. Thirteen of the 14 studies evaluated 1,25 dihydroxyvitamin D levels, three of these also evaluated 24,25 dihydroxyvitamin D (2 studies) and/or 25 hydroxyvitamin D levels (3 studies), and one study evaluated only 25 hydroxyvitamin D levels. Each of the 13 studies noted that 1,25 dihydroxyvitamin D levels were lower with decreased kidney function. The two studies evaluating 24,25 dihydroxyvitamin D levels noted lower levels with lower kidney function. The four studies evaluating 25 hydroxyvitamin D levels showed conflicting results.

These data confirm that 1,25 dihydroxyvitamin D levels are lower in patients with decreased kidney function. There is limited information to suggest that 24,25 dihydroxyvitamin D levels are lower in patients with decreased kidney function. The studies do not provide data on the association between level of kidney function and 25 hydroxyvitamin D levels.

Bone histology is abnormal in the majority of patients with kidney failure (Table 98) (C). Six articles that related bone biopsy findings to level of kidney function among patients with chronic kidney disease not yet on dialysis were reviewed. The sample sizes ranged from 20 to 176 individuals. The levels of kidney function ranged from nearly normal (creatinine clearance of 117 mL/min) to the initiation of dialysis. Among patients with kidney failure immediately prior to initiation of dialysis, 98% to 100% had abnormal bone histology, with the majority of the biopsies showing either osteitis fibrosa or adynamic bone disease[389,433] (data not shown). The studies evaluating patients with varying levels of kidney function demonstrated: (1) a direct relationship between bone mineralization and kidney function[415,421]; (2) an inverse relationship between kidney function and bone osteoid/resorption[415]; or (3) a higher prevalence of abnormalities on bone biopsy (osteomalacia, resorption, osteoid) among patients with reduced kidney function.[392,419,434,435] In two studies of patients with varying levels of kidney function not yet receiving treatment with vitamin D agents, one[374] with 76, the other[392] with 176 subjects, 75% to 85% had significant abnormalities on bone biopsy. The majority had osteitis fibrosa, with or without osteomalacia.

There were 4 studies of bone densitometry reviewed for this topic, which demonstrated that bone mineralization is reduced with decreased kidney function. One study presented the results as a higher prevalence of reduced bone mineral content with decreased levels of kidney function. Other studies noted a reduced bone mineral content among patients with decreased kidney function compared to controls. This is insufficient evidence to make firm statements regarding the

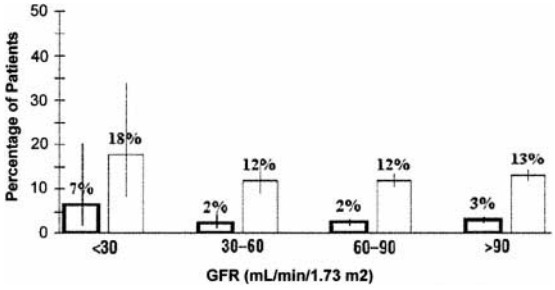


Fig 40. Prevalence of hypocalcemia (adjusted for albumin) versus GFR. These data are based on the results of 446 patients enrolled in the Canadian Multicentre Longitudinal Cohort study of patients with chronic kidney disease. All patients were referred to nephrologists between 1994 and 1997. No patient was receiving erythropoietin therapy at the time of enrollment, and no patient had an AV fistula. GFR is calculated using the modified MDRD formula. Hypocalcemia was defined as serum calcium levels (adjusted for albumin) of <8.5 mg/dL. Adapted and reprinted with permission.[288]

Table 96. Serum Phosphate and Kidney Function

Author, Year	No. of Subjects	Applicability	GFR Range (mL/min/1.73 m^2) 0 30 60 90 120	Results*	Quality
Martinez,[405] 1997	157	♦♦♦		⇔	●
Pitts,[406] 1988	72	♦♦♦		⇩	●
St. John,[407] 1992	51	♦♦♦		⇩	●
Reichel,[408] 1991	85	♦♦		⇔	●
von Lilienfeld-Toal,[409] 1982	81	♦♦		⇩	●
Cheung,[410] 1983	39	♦♦♦	S_{Cr} 3.4 ±0.3 mg/dL	⇩	○
Fajtova,[411] 1995	39	♦♦♦		⇩	○
Coburn,[429] 1973	256	♦♦	S_{Cr} 11.1 ±7.6 mg/dL	⇩	○
Rix,[412] 1999	202	♦♦		⇩	○
Yumita,[413] 1996	195	♦♦	S_{Cr} <1 –>8 mg/dL	⇩	○
Christensen,[414] 1977	188	♦♦		⇔	○
Coburn,[430] 1969	126	♦♦		⇩	○
Massry,[427] 1973	105	♦♦		⇩	○
Kates,[378] 1997	84	♦♦		⇩	○
Saha,[417] 1994	50	♦♦		⇩	○
Messa,[418] 1995	43	♦♦		⇔	○
Coen,[420] 1989	32	♦♦	S_{Cr} 6.5 ±2.9 mg/dL	⇩	○
Tougaard,[421] 1977	24	♦♦		⇩	○
Madsen,[422] 1976	15	♦♦		⇔	○
Arata,[424] 1976	31	♦♦		⇩	○
Slatopolsky,[428] 1968	30	♦♦		⇔	○

* ⇩ = higher GFR associated with lower serum phosphate (statistically significant);
⇩ = higher GFR associated with lower serum phosphate;
⇔ = GFR *not* associated with serum phosphate.

relationship between bone density and level of kidney function.

LIMITATIONS

These guidelines are limited by the inability to provide a definitive quantitative or semi-quantitative assessment of the relationship between level of kidney function and marker of bone disease. This is in part due to the lack of comparability of many of the studies given the diversity of the laboratory assays or tests for the particular abnormality. This was particularly true for PTH and

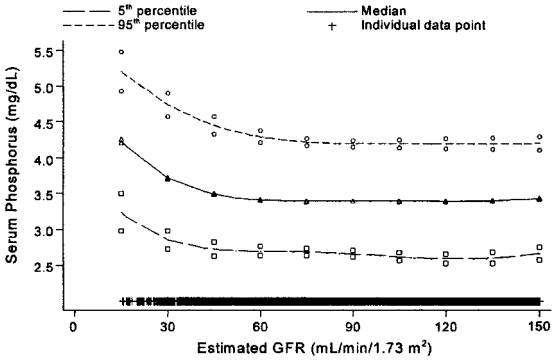


Fig 41. Serum phosphorus levels versus GFR (NHANES III). Median and 5th and 95th percentiles of serum phosphorus among adult participants age 20 years and older in NHANES III, 1988 to 1994. Values are adjusted to age 60 years using a polynomial quantile regression. The estimated GFR for each individual data point is shown with a plus near the abscissa. 95% confidence intervals at selected levels of estimated GFR are demarcated with triangles, squares, and circles.

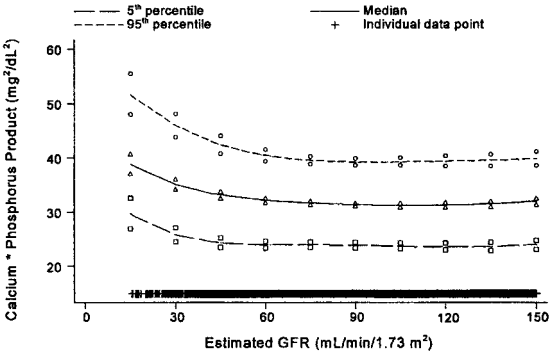


Fig 43. Calcium-phosphorus product percentiles by GFR (NHANES III). Median and 5th and 95th percentiles of serum calcium-phosphorus product, adjusted for serum albumin, among adult participants age 20 years and older in NHANES III, 1988 to 1994. Values are adjusted to age 60 years using a polynomial quantile regression. The estimated GFR for each individual data point is shown with a plus near the abscissa. 95% confidence intervals at selected levels of estimated GFR are demarcated with triangles, squares, and circles.

vitamin D_3 (calcitriol) levels, but also applies to bone densitometry. Similarly, the interpretation of bone biopsies and radiographic tests likely has a range of error, in this case related to inter-observer variability.

In addition, as with most of the Guidelines in Part 6, the results are difficult to compare as they use different measures for kidney function: measured GFR or creatinine clearance, estimation equations for GFR or creatinine clearance, or simply serum creatinine.

Lastly, many of the studies involved only few patients with GFR >60 mL/min/1.73 m^2. This leads to the extrapolation of the results from other studies to such patients with variable levels of confidence for the various markers.

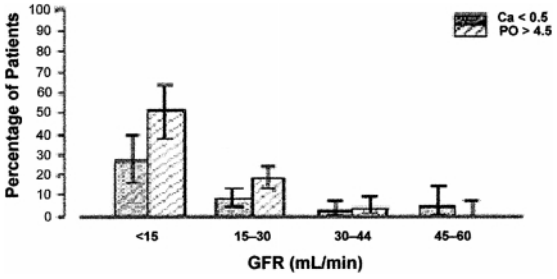


Fig 42. Prevalence of low calcium and high phosphate by GFR category. These data are based on the results of 446 patients enrolled in the Canadian Multicentre Longitudinal Cohort study of patients with chronic kidney disease. All patients were referred to nephrologists between 1994 and 1997. No patient was receiving erythropoiten therapy at the time of enrollment, and no patient had an AV fistula. Intact molecule PTH assay is reported in picomoles per liter, and GFR is calculated using the modified MDRD formula (using age, race, gender, and serum creatinine). Low calcium levels are defined as levels 8.5 mg/dL, adjusted for albumin, and high phosphate levels are defined as >4.5 mg/dL. Adapted and reprinted with permission.[288]

CLINICAL APPLICATIONS

The data reviewed here suggest that abnormalities of bone/mineral metabolism begin to occur early in kidney disease; thus, the implications are that:

- Indices of bone/mineral metabolism should be measured when there is indication of any level of kidney dysfunction—PTH, phosphorus and ionized calcium levels are the most commonly used biomarkers.
- Biomarkers of bone/mineral metabolism should be followed longitudinally in individual patients as it is expected that abnormalities may develop or become more severe as kidney function deteriorates.
- There are currently no convincing data to suggest that there is benefit to routinely obtaining bone biopsies or bone densitometry. Bone biopsy may be indicated if

Table 97. Vitamin D_3 and Kidney Function

Author, Year	No. of Subjects	Applicability	GFR Range (mL/min/1.73 m^2) 0 30 60 90 120	Results*	Quality
Pitts,[406] 1988	72	♦♦♦		⬆	●
St. John,[407] 1992	51	♦♦♦		⬆ (1,25) ⇔ (25)	●
Reichel,[408] 1991	85	♦♦		⬆ (1,25)	●
Ishimura,[431] 1999	76	♦♦♦		⬆ (1,25; 24,25) ⇔ (25)	○
Cheung,[410] 1983	39	♦♦♦	S_{Cr} 3.4 ±0.3 mg/dL	⬆ (1,25)	○
Fajtova,[411] 1995	39	♦♦♦		⬆ (1,25)	○
Rix,[412] 1999	202	♦♦		⬆ (1,25)	○
Yumita,[413] 1996	195	♦♦	S_{Cr} <1–>8 mg/dL	⬆ (1,25)	○
Kates,[378] 1997	84	♦♦		⬆ (1,25)	○
Nielsen,[432] 1976	81	♦♦		⬇ (25)	○
Saha,[417] 1994	50	♦♦		⇧ (1,25; 24,25; 25)	○
Messa,[418] 1995	43	♦♦		⬆ (1,25)	○
Tessitore,[419] 1987	41	♦♦		⬆ (1,25)	○
Coen,[420] 1989	32	♦♦	S_{Cr} 6.5 ±2.9 mg/dL	⬇ (1, 25) ⇔ (25)	○

* ⬆ = higher GFR associated with higher level of indicated Vitamin D_3 (statistically significant);
⇧ = higher GFR associated with higher level of indicated Vitamin D_3;
⇔ = GFR *not* associated with level of indicated Vitamin D_3;
⬇ = higher GFR associated with lower level of indicated Vitamin D_3.

there is symptomatic disease or if "aggressive" interventions such as parathyroidectomy or desferoxamine therapy are being contemplated.

The applications suggested above are based on review of the available literature presented herein and on opinion. The suggestion to follow the biomarkers over time is based on the hypothesis that a change in some of these biomarkers may occur even when there is no change in GFR. In fact, changes in the biomarkers may provide an earlier indication of worsening kidney function.

Treatment recommendations are beyond the scope of this guideline, and will be addressed elsewhere (see K/DOQI Bone Metabolism and Disease in CKD Guidelines).

IMPLEMENTATION ISSUES

Medicare at present does not cover payment for PTH levels for screening for hyperparathyroidism among patients with chronic kidney disease, unless they have a diagnosis specific to hyperparathyroidism.[437] Calcium and ionized calcium tests are also not covered for the evaluation of patients with chronic kidney disease, while phosphate and alkaline phosphate tests are covered.[437]

Clearly, since the evidence shows that there may be elevation in the PTH level in the setting of normal phosphorus and calcium levels, and high PTH levels are deleterious to bone and non-osseous tissue, policies regarding testing and reimbursement need to be reassessed.

Table 98. Bone Disease and Kidney Function

Author, Year	Measurement	No. of Subjects	Applicability	GFR Range (mL/min/1.73 m²) 0 30 60 90 120	Results*	Quality
Biopsy Studies:						
Hamdy,[392] 1995	Abnormal bone histology	176	↑↑		⇩	●
Coen,[435] 1996	Bone disease severity by biopsy	76	↑↑		⇩	●
Malluche,[415] 1976	Osteoid %	72	↑↑		⇩	●
Malluche,[415] 1976	Osteoclastic surface resorption	72	↑↑		⇩	●
Bedani,[423] 1985	Osteoclastic surface resorption	61	↑↑		⇩	○
Tessitore,[419] 1987	Proportion with osteomalacia	41	↑↑		⇔	●
Tessitore,[419] 1987	% bone resorption	41	↑↑		⇩	●
Suzuki,[434] 1980	Osteoid surface area	20	↑↑		⇩	●
Radiology Studies:						
Madsen,[436] 1978	Bone mineral content	279	↑↑↑		⇧	●
Nielsen,[432] 1976	Bone mineral content	81	↑↑		⇩	●
Tougaard,[421] 1977	Bone mineral content	24	↑↑		⇧	●
Bedani,[423] 1985	Acro-osteolysis	61	↑↑		⇩	○
Rix,[412] 1999	Hip DEXA	202	↑↑		⇧	●
Other Studies:						
Tougaard,[421] 1977	Phosphorus: hydroxyproline ratio	24	↑↑		⇧	●

Bold horizontal lines divide studies by type of measurement used.

* ⇧ = higher GFR associated with higher level of indicated bone measurement (statistically significant);
⇔ = GFR *not* associated with indicated bone measurement;
⇩ = higher GFR associated with lower level of indicated bone measurement (statistically significant);
⇩ = higher GFR associated with lower level of indicated bone measurement.

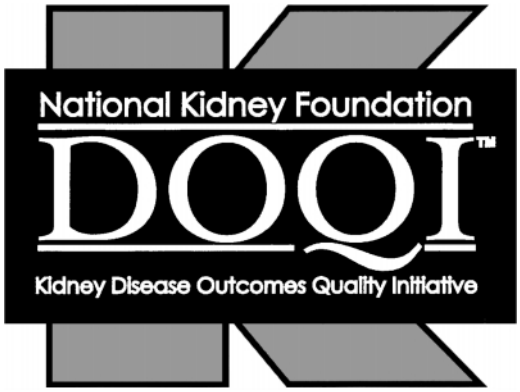
RESEARCH RECOMMENDATIONS

Much of the available information regarding abnormalities of mineral metabolism is derived from studies of patients with kidney failure or severely decreased kidney function. Clearly, more information is needed on the abnormalities of bone mineral metabolism among patients with earlier stages of chronic kidney disease. Moreover, research on outcomes related to abnormal mineral metabolism or bone disease is lacking in both patients with mildly, as well as severely decreased kidney function. In addition to bone complications, there is increasing evidence relating abnormal calcium-phosphorus metabolism and hyperparathyroidism to vascular calcification and cardiovascular complications.

The relationship between levels of the available markers, and levels of kidney function, should be more accurately characterized. In addi-

tion, the relationship between such levels and kidney function should be separately studied among patients with additional risks of bone complications, that is, patients treated for prolonged periods with corticosteroids and transplant recipients.

Research should also focus on the impact of interventions on levels of available markers and outcomes, specifically of interest would be comparing patients cared for by nephrologists with those not under the care of nephrologists, patients treated for some specified period of time for hyperparathyroidism compared to those not treated, and patients treated with corticosteroids compared to those never treated with such drugs.



GUIDELINE 11. ASSOCIATION OF LEVEL OF GFR WITH NEUROPATHY

Neuropathy develops during the course of chronic kidney disease and may become symptomatic.

- **Patients with chronic kidney disease should be periodically assessed for central and peripheral neurologic involvement by eliciting symptoms and signs during routine office visits or exams.**
- **Specialized laboratory testing for neuropathy in patients with chronic kidney disease is indicated only in the presence of symptoms.**

BACKGROUND

Neuropathy is a common complication of patients with kidney failure.[438-440] Neuropathy may be manifested as encephalopathy, peripheral polyneuropathy, autonomic dysfunction, sleep disorders, and, less commonly, peripheral mononeuropathy. Occurrence of neuropathy is related to the level of kidney function, but not the type of kidney disease. However, there are certain causes of chronic kidney disease that also affect the central and/or peripheral nervous system. These are amyloidosis, diabetes, systemic lupus erythematosus, polyarteritis nodosa, and hepatic failure.[438,439] In addition, there are congenital disorders that affect both the kidneys and nervous system, such as Von Hippel Lindau disease, Wilson's disease, and Fabry's disease.[438]

The pathophysiology of uremic neuropathy is not well understood. Levels of urea, creatinine, PTH, "middle molecules," and others have been correlated with reduction of nerve conduction velocity (NCV) and peripheral manifestations of neuropathy.[438,439] In advanced stages there is evidence of histopathological damage with axonal degeneration and secondary demyelination of peripheral nerves.[438]

RATIONALE

Markers of Neuropathy

Uremic neuropathy may affect the central, peripheral, or autonomic nervous systems. Early uremic encephalopathy may present with fatigue, impaired memory, or concentration. With more advanced uremia delirium, visual hallucinations, disorientation, convulsions, and coma may develop.[438] Generally, uremic polyneuropathy is a symmetrical, mixed sensory and motor polyneuropathy, with distal nerves more severely affected. Patients may complain of pruritus, burning, muscle irritability, cramps, or weakness.[438,439] Autonomic function abnormalities include impaired heart rate and blood pressure variability in response to respiratory cycle, postural change, and valsalva.

Signs on examination include muscle atrophy, loss of deep tendon reflexes, poor attention span, impaired abstract thinking, abnormal or absent reflexes (in particular ankle jerk), and impaired sensation (vibratory, light touch pressure, and pain).[438,439] Later signs include meningismus, myoclonus, and asterixis.[438] Electroencephalography (EEG) has generalized slowing, and bilateral spike and wave complexes have been described in up to 14% of patients, even in the absence of evident clinical seizure activity.[438] EEG measures of sleep also are disturbed in dialysis patients.[441] CT scan or MRI is not helpful, though there may be cerebral atrophy.[438,442-444] The most sensitive test for detection of asymptomatic peripheral neuropathy is slowed sensory NCV; although motor NCV is slowed, there is a wide intra-individual day-to-day variation, and these findings occur with more advanced kidney dysfunction.[438,439,445]

Strength of Evidence

Neuropathy develops during the course of chronic kidney disease (R). Neuropathy is present in up to 65% of patients at the initiation of dialysis[438,439]; thus, it must begin to develop during an earlier phase of kidney disease. Symptoms of peripheral neuropathy generally do not present unless the GFR is under 12 to 20 mL/min, or uremia has been present for at least 6 months.[438,439] Encephalopathy may become evident with less prolonged impairment of kidney function and can be seen with acute decline in GFR, although the correlation of central nervous system manifestations with level of kidney func-

tion is poor.[438] Autonomic neuropathy is present in 20% to 80% of patients with diabetic nephropathy,[442,444] in 66% of patients with severely impaired kidney function (creatinine clearance <8 mL/min), and in 50% of patients on dialysis.[443]

Objective findings of peripheral neuropathy as evaluated by NCV studies are present in 15% to 85% of individuals with decreased GFR.[446-449] Sensory NCV is decreased in over 90% of patients, whereas motor NCV is decreased in only 40%.[445] Among patients on dialysis, objective evidence of neuropathy is present in 50% to 100%,[440,446] and the prevalence appears to increase with duration of dialysis.[440]

Objective evidence of central nervous system (CNS) dysfunction is not uniformly evident. EEG has been described to be minimally abnormal in a "small percentage" of patients[445] or as slowed in most patients,[450] with the degree of slowing more pronounced with more advanced dysfunction. EEG findings have been reported to improve after initiation of dialysis or with transplant.[450] Tests of cognitive function were abnormal in all patients and were more impaired with increasing creatinine. Transplant and dialysis patients had somewhat better, but not normal, scores.[450]

Treatment with dialysis improves the more severe symptoms and findings of CNS involvement and improves the symptoms of polyneuropathy; however, NCV remains abnormal in up to 60% to 80%.[440] The symptoms and findings of peripheral neuropathy are dramatically improved by transplantation.[438]

Neuropathy is associated with worse outcomes in chronic kidney disease (R). No articles were found that specifically related the presence of neuropathy to other outcomes among patients with chronic kidney disease. However, it is self-evident that impaired cognition and sleep, dysesthesias, and impaired autonomic function would at least lead to reduced quality of life and inability to function normally. If the neuropathy leads to skin ulcers, then certainly this would result in objective morbidity and potentially mortality. Advanced encephalopathy may result in seizures, coma, and death.[438]

Objective findings of neuropathy can be detected before symptoms arise (C, R). Several of the articles reviewed note that the majority of patients who have abnormalities in tests of nervous system function are asymptomatic.[445,447,448] However, abnormalities are more profound among patients with symptoms.[447,448]

Onset and severity of neuropathy is associated with the level of GFR; there is insufficient evidence to define a specific threshold level of GFR that is associated with an increased prevalence or severity of neuropathy (C). The articles reviewed varied greatly in the levels of kidney function assessed, as well as in the measure of kidney function used, as some used only serum creatinine levels and other used GFR or creatinine clearance. Most studies demonstrated a relationship between kidney function and the particular marker of neuropathy. However, several studies only compared the particular marker with the normal or reference standard for the test or compared grouped data on patients with kidney disease with controls or patients on dialysis/transplant without providing data at various levels of kidney function. Summaries of the studies reviewed are presented in Tables 99 and 100.

Nerve conduction velocity (NCV) is slower in patients with decreased GFR (Table 99) (C). There were 6 studies relating NCV to level of kidney function. The studies had sample sizes ranging from 40 to 210 subjects, with 29 to 72 patients with decreased kidney function not yet on dialysis. All but one[450] of the studies showed that NCV was decreased below normal levels among patients with decreased kidney function. In three of the studies, the correlation between kidney function level and NCV was significant; in the other two correlation was suggested but lacked statistical significance. A threshold level of kidney function for abnormal motor NCV was only mentioned or deducible from three studies. Below a GFR of 8 to 13[446,448] or serum creatinine above 7 to 8 mg/dL,[445] 50% or more patients with decreased kidney function had abnormal NCV. The threshold level at which 50% or more of patients have abnormal sensory NCV velocity was evaluated in only two studies and noted to be approximately 8 to 20 mL/min.[445,448]

These data generally confirm that NCV is decreased among patients with decreased kidney function. The reviewed studies do suggest a correlation between level of GFR and NCV, but they

Table 99. Nerve Conduction Velocity and Kidney Function

Author, Year	No. of Subjects	Applicability	GFR Range (mL/min/1.73 m²) 0 30 60 90 120	Results*	Quality
Teschan,[450] 1979	177	↑↑	S_{Cr} 2–29 mg/dL	⇔	O
Di Paolo,[445] 1982	129	↑↑		↑	O
Savazzi,[451] 1980	100	↑↑		⇧	O
Nielsen,[448] 1973	56	↑↑		↑	O
Goel,[447] 1978	40	↑↑		⇔	O
Knoll,[449] 1980	210	↑	S_{Cr} 1–12 mg/dL	⇔	O

* ↑ = higher GFR associated with faster nerve conduction velocity (statistically significant);
⇧ = higher GFR associated with faster nerve conduction velocity;
⇔ = GFR *not* associated with nerve conduction velocity.

do not offer sufficient information to convincingly demonstrate a threshold level of GFR at which NCV becomes abnormal.

Memory and cognition are impaired in patients with decreased GFR (Table 100) (C). Only one study was found that evaluated memory and cognition among patients with decreased kidney function prior to the availability of erythropoietin.[450] In this study of 177 subjects, of whom 72 had decreased kidney function not yet on dialysis, several cognitive functions were assessed, including sustained attention, selective attention, speed of decision-making, short-term memory, and mental manipulation of symbols. Each of these test measures was significantly lower among patients with decreased kidney function, correlated with level of dysfunction, and was improved to varying degrees among patients on dialysis and to a greater degree among patients with a kidney transplant.

Autonomic function is impaired in patients with decreased GFR (Table 101) (C). Only three studies were found that objectively evaluated autonomic function among patients with kidney disease. These studies had between 42 and 123 subjects and between 21 and 67 patients

Table 100. Miscellaneous Neurological Measurements and Kidney Function

Author, Year	Measurement	No. of Subjects	Applicability	GFR Range (mL/min/1.73 m²) 0 30 60 90 120	Results*	Quality
Teschan,[450] 1979	EEG slowing	177	↑↑	S_{Cr} 2–29 mg/dL	↓	O
Teschan,[450] 1979	Cognition/memory test score	177	↑↑	S_{Cr} 2–29 mg/dL	↑	O
Goel,[447] 1978	Peripheral neuropathy symptoms	40	↑↑		⇔	O
Knoll,[449] 1980	Reflex response latency	210	↑	S_{Cr} 1–12 mg/dL	↑	O
Di Paolo,[445] 1982	Abnormal EMG	129	↑↑		100%	O

* ↑ = higher GFR associated with higher level of indicated neurological measurement (statistically significant);
⇔ = GFR *not* associated with indicated cognitive measurement;
↓ = higher GFR associated with lower level of indicated neurological measurement (statistically significant).

Abbreviations: EEG, electroencephalogram; EMG, electromyography

Table 101. Autonomic Function and Kidney Function

Author, Year	Measurement	No. of Subjects	Applicability	GFR Range (mL/min/1.73 m^2) 0 30 60 90 120	Results*	Quality
Campese,[443] 1981[a]	HR responses	112			⬆	O
Weinrauch,[442] 1995	HR responses	42			⇔	O
Stemer,[444] 1997	HR responses	123			⇧	O
Campese,[443] 1981[a]	BP responses	112			⬆	O
Weinrauch,[442] 1995	Day:night BPI	42			⇔	O

Bold horizontal lines divide studies by measurement used.

* ⬆ = higher GFR associated with higher level of indicated autonomic function measurement (statistically significant);
⇧ = higher GFR associated with higher level of indicated autonomic function measurement;
⇔ = GFR *not* associated with level of indicated autonomic function measurement.

[a] Study included two separate populations.

Abbreviations: BP, blood pressure; BPI, blood pressure index; HR, heart rate

with decreased kidney function not yet on dialysis. Each of these studies noted that autonomic function was impaired in more than 50% of patients with chronic kidney disease; however, only one of them found an association between level of kidney function and measures of autonomic nerve function.

The results of these studies cannot be extrapolated with confidence to the general population of patients with chronic kidney disease, as two were limited to patients with diabetes[442,444] and thus confounded by the neuropathy ascribable to diabetes, and the third only had patients with very decreased kidney function (GFR <8 mL/min) or on dialysis.[443]

Symptoms of neuropathy, including sleep disturbances, are increased in patients with decreased GFR (C). Symptoms or clinical signs of peripheral neuropathy were evaluated or mentioned in four of the six studies of peripheral neuropathy reviewed for this guideline.[445-448,450] The method of ascertaining the presence of symptoms or clinical findings was mentioned in only one of these studies[447] as a "detailed neurological examination was carried out to find. . .evidence of clinically manifest neuropathy." The prevalence of symptoms or clinical findings ranged from 0% to 52%. Individuals with clinical symptoms had a greater reduction in NCV as compared to those without such symptoms in 2 studies,[446,448] whereas there was no significant correlation between NCV and symptoms in one of the studies.[447] None of the studies commented on the correlation between symptoms and level of kidney function; however, from a single study it was estimated that patients with symptoms had a lower mean level of kidney function (GFR = 6 mL/min) than patients without symptoms (GFR = 16 mL/min).[446]

The reviewed studies do not offer sufficient information to convincingly delineate a progressive increase in prevalence of symptoms with decreasing GFR.

LIMITATIONS

Several of the reviewed articles included patients who had started dialysis or received a kidney transplant; information on these patients was used for background information and comparison. More articles than were reviewed were found with the literature search, but were not exhaustively reviewed as preliminary review suggested the lack of or inability to extract the necessary information. This may have led to the omission of some articles that may have provided further information.

These guidelines are limited by the inability to provide a definitive quantitative or semi-quantitative assessment of the relationship between level

of kidney function and markers of neuropathy. This is in part due to the dearth of studies, the use of different measures of kidney function, the limited presentation of methods, and the failure to present adequate correlation data. In particular, there was extremely limited information on cognitive function and symptoms of neuropathy.

Lastly, many of the studies involved only a limited number of patients with mildly to moderately decreased kidney function, and two of the studies were limited to diabetics, confounding the results with the presence of diabetic neuropathy.

CLINICAL APPLICATIONS

The data reviewed here suggest that symptoms of neuropathy begin to occur at very low levels of GFR. The inconclusive evidence presented herein has the implications that:

- Indices of neuropathy are not useful to monitor progression of chronic kidney disease.
- Symptoms or indices of neuropathy are evidence of kidney failure, and may be useful to determine need to initiate dialysis.
- There are currently no convincing data to suggest that there is benefit to obtaining nerve conduction studies or nerve biopsies in asymptomatic patients.

The applications suggested above are based on review of the available literature presented herein and opinion based on others' reviews of the problem. Treatment and assessment recommendations are beyond the scope of this guideline.

IMPLEMENTATION ISSUES

The only implementation issue arising from this guideline is to provide education regarding the prevalence of neuropathy, and the need to elicit symptoms and signs of this condition during routine office visits.

RESEARCH RECOMMENDATIONS

Much of the available information regarding neuropathy is derived from studies of patients with kidney failure. More information on neuropathy among patients with chronic kidney disease with earlier stages of chronic kidney disease may provide other means to follow progression of chronic kidney disease. In addition, if neuropathy were to be more carefully described and noted to have a high prevalence in earlier stages of chronic kidney disease and a relationship to kidney function, treatments to delay its progression could be considered.

The relationship between subjective and objective measures of neuropathy, and levels of kidney function, should be more accurately characterized. In addition, the relationship between neuropathy and kidney function should be separately studied among patients with additional risks of neuropathy, such as diabetics and patients with amyloidosis.

GUIDELINE 12. ASSOCIATION OF LEVEL OF GFR WITH INDICES OF FUNCTIONING AND WELL-BEING

Impairments in domains of functioning and well-being develop during the course of chronic kidney disease and are associated with adverse outcomes. Impaired functioning and well-being may be related to sociodemographic factors, conditions causing chronic kidney disease, complications of kidney disease, or possibly directly due to reduced GFR.

- **Patients with GFR <60 mL/min/1.73 m^2 should undergo regular assessment for impairment of functioning and well-being:**
  - **To establish a baseline and monitor changes in functioning and well-being over time**
  - **To assess the effect of interventions on functioning and well-being.**

BACKGROUND

When there is no cure for a chronic illness, an essential healthcare goal must be to maximize quality of life. The purpose of this guideline is to identify stages and complications of kidney disease that place adult patients at greater risk for reduced quality of life. This guideline is not intended to cover all the quality of life concerns that apply to children and adolescents, nor is it intended to recommend interventions to improve quality of life in any age group. For the purpose of this guideline, concepts that embody pertinent components of quality of life will be referred to as "functioning and well-being." Recent studies show that the functioning and well-being of individuals with chronic kidney disease is related to such factors as: late referral and inadequate pre-dialysis care[80]; symptoms; effects of illness on physical, psychological, and social functioning; and satisfaction with health and care.[452] Complications of chronic kidney disease, such as anemia, malnutrition, bone disease, neuropathy, and comorbid conditions, such as diabetes and cardiovascular disease, can negatively affect functioning and well-being. To improve functioning and well-being, patients must be referred sooner and complications and comorbid conditions must be managed appropriately.

This guideline describes the association between the level of kidney function and domains of functioning and well-being in patients with chronic kidney disease. One must analyze the full continuum of stages of chronic kidney disease to understand the risks for compromised functioning and well-being. Armed with this knowledge, clinicians can more quickly identify stages of chronic kidney disease at which deficits are likely to occur and develop strategies to treat higher risk patients and ameliorate or eliminate deficits before they become severe or irreversible.

RATIONALE

Definitions

Health status outcomes experts recommend defining "quality of life" to include variables that health professionals can identify, quantify, and modify: (1) health status (signs and symptoms, lab values, death); (2) functional status (physical, mental, social, and role functioning), and (3) well-being (energy/fatigue, pain, health perceptions, and satisfaction).[453,454] Self-report is preferable to staff report since outcomes are dependent on the lived experience and expectations of the individual patient.

Difficulties in measuring this poorly understood concept have led researchers in the articles reviewed to study several variables using different methods and instruments (Table 102). Use of different instruments has impeded comparing findings, interpreting results, and drawing conclusions.

Strength of Evidence

Indices of functioning and well-being are impaired in chronic kidney disease (R). Dialysis patients report significantly more bodily pain, lower vitality, poorer general health, greater physical, mental, and social dysfunction, and greater limitations in their ability to work and participate in activities due to their health and emotions than the US reference norm. At least 25% are depressed.[455] Dialysis patients' exercise capacity is significantly worse than that

Table 102. Domains of Functioning and Well-being Measured by Specific Instruments

Instrument	Symptoms & Health Perception	Physical Function	Mental Health Function	Employment	Social Function
Beck Depression Inventory (BDI)	Depressive	No	Yes	Yes	Yes
Center for Epidemiological Studies-Depression (CES-D)	Yes	No	Yes	No	No
Cognitive Depression Index (CDI)	No	No	Yes	No	No
ESRD Severity Coefficient	Yes	No	No	No	No
EuroQol	Yes	Yes	Yes	Yes	Yes
Health Index (HI)	Yes	Yes	Yes	No	No
Illness Effects Questionnaire (IEQ)	Yes	No	Yes	No	Yes
Karnofsky Performance Scale (KPS)	Yes	Yes	No	Yes	Yes
MOS Short Form 36 (SF-36)	Yes	Yes	Yes	Yes	Yes
Multidimensional Scale of Perceived Social Support (MSP)	No	No	No	No	Yes
NHANES Adult Questionnaire (NHANES)	Yes	Yes	Yes	Yes	Yes
Quality of Well-being Scale (QWB)	Yes	Yes	Yes	Yes	Yes
Rand Health Insurance Experiment instrument (RHIE)	No	Yes	Yes	Yes	Yes
Satisfaction with Life Scale (SLS)	No	No	Yes	No	No
Sense of Coherence Scale	No	No	Yes	No	No
Sickness Impact Profile (SIP)	Yes	Yes	Yes	Yes	Yes
Social Adjustment Scale Self-Report (SAS-SR)	No	Yes	Yes	Yes	Yes
State Trait Anxiety Inventory (STAI)	Anxiety	No	Yes	No	No
Symptom Checklist-90R (SCL-90R)	Yes	No	Yes	No	No

of healthy controls.[456] Kidney failure negatively affects sense of control and health outlook in those on dialysis.[457] About 39% of those who worked full or part-time 6 months before dialysis do not continue working when they start dialysis.[4] Elderly people on dialysis engage in few previously enjoyed activities outside their homes and many leave home only for dialysis because of weakness.[458]

Impairment in indices of functioning and well-being are associated with worse outcomes in chronic kidney disease (R). Impaired functioning and well-being in dialysis patients is linked to increased risk of death and hospitalization while improvement in scores has been associated with better outcomes. Patients with SF-36 Physical Component Summary (PCS) scores <34.6 had a 2.03 relative risk of dying and a 1.67 relative risk of being hospitalized. Each 5-point improvement in PCS scores was associated with 10% longer survival and 6% fewer hospital days. On the SF-36, a Mental Health scale score ≤ 52 and a Mental Component Summary (MCS) score ≤ 42 indicate depression. Each 5-point improvement in the MCS score is associated with 2% fewer hospital days.[455]

Impairment in functioning and well-being are associated with sociodemographic characteristics (R). Low income and low education were associated with greater impairments in functioning and well-being in patients with chronic kidney disease.[459]

Impairment in functioning and well-being may be due to conditions that cause chronic kidney disease (such as diabetes or hypertension) or complications of decreased GFR (such as anemia, malnutrition, bone disease, or neuropathy) (R). Hypertension, diabetes with angina, prior cardiac infarction,[460] osteoporosis,

bone fractures,[461] and malnutrition[462] have been shown to impair functioning and well-being in those with no known kidney disease. Among veterans with diabetes, neuropathy and kidney disease have been associated with the greatest decrease in functioning and well-being.[463]

Anemia has been linked to poor functioning and well-being in patients with severely decreased GFR and dialysis patients, and improving anemia with erythropoietin has been linked to improvement in functioning and well-being.[284,464-468]

Indices of functioning and well-being are related to the level of GFR; below a GFR of approximately 60 mL/min/1.73 m^2, there is a higher prevalence of impairments in indices of functioning and well-being (S, C). Data from cross-sectional studies and baseline data from longitudinal studies were reviewed to assess the relationship between level of kidney function and level of functioning and well-being. Populations studied include those with decreased kidney function, including those with functioning transplants, and dialysis patients when compared with healthy subjects or kidney transplant recipients. While much of the data on functioning and well-being related to outcomes have been obtained in dialysis patients, there is convincing evidence that abnormalities in functioning and well-being begin earlier in chronic kidney disease and may well be related to declining GFR.

Symptoms (Table 103 and Fig 44). Reduced kidney function is associated with increasing symptoms such as tiring easily, weakness, low energy, cramps, bruising, bad tasting mouth, hiccoughs, and poor odor perception. This is true in patients with native kidney disease and those with kidney transplants. Diabetic dialysis and transplant patients are more likely to report poor health than dialysis or transplant patients who do not have diabetes.

Table 103. Symptoms & Health Perception and Kidney Function

Author, Year	Instrument/ QoL Parameters	No. of Subjects	Applicability	GFR Range (mL/min/1.73 m^2) 0 30 60 90 120	Results*	Quality
Rocco,[469] 1997	SCL-90R MDRD Symptom Form: Symptoms	1,284	♀♀		⬆	●
Korevaar,[470] 2000	SF-36: Pain, General health EuroQol: Pain, Discomfort, Health valuation	301	♀♀		⬆	●
Shidler,[471] 1998	IEQ: Perception of illness	50	♀♀		⇔	●
Klang,[472] 1996	HI: General health, Fatigue, Energy, Sleep problems, Mobility, Mood, Loneliness	38	♀♀		⬆	●
Harris,[459] 1993	SIP: Perceived illness	360	♀♀		⇔	○
Fujisawa,[473] 2000	SF-36: General health	231	♀♀	S_{Cr} 1.2 ±0.5 mg/dL	⬆	○
Griep,[474] 1997	Odor perception	202	♀♀		⬆	○
Sacks,[475] 1990	IEQ: Perception of illness	73	♀♀	S_{Cr} 5.4 ±3.4 mg/dL	⬆	○
Manninen,[476] 1991	Satisfaction with health	226	♀	ND	⬆ (transplant vs. dialysis)	○

* ⬆ = higher GFR associated with better functioning and well-being (statistically significant);
⇔ = GFR *not* associated with level of functioning and well-being.

Abbreviations: SCL-90R, Symptom Checklist-90R; SF-36, Medical Outcomes Study Short Form 36; IEQ, Illness Effects Questionnaire; HI, Health Index; SIP, Sickness Impact Profile

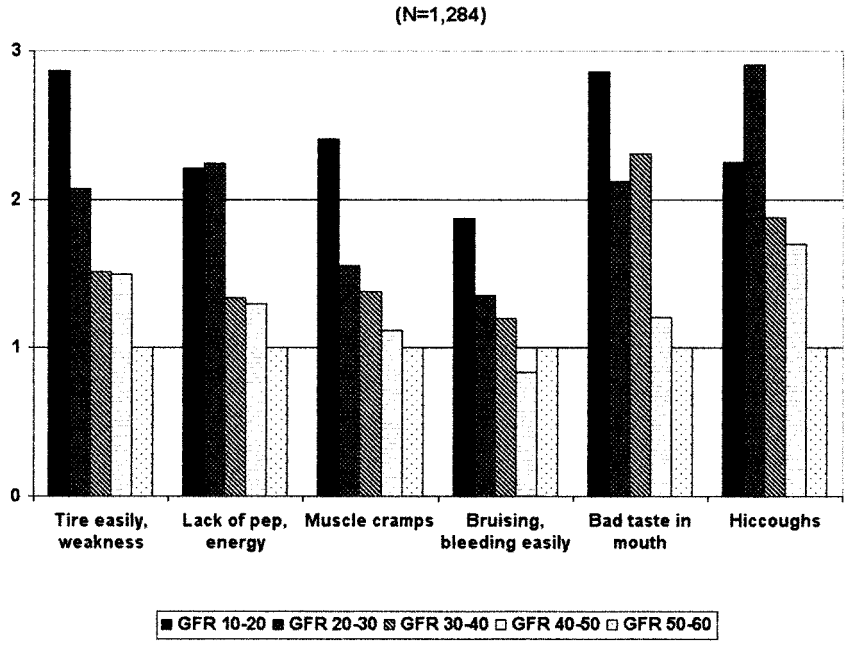


Fig 44. Kidney function (GFR) and odds of having symptoms affecting quality of life and well-being in the MDRD Study, controlled for age, gender, race, kidney diagnosis, education, income, and smoking status. Reprinted with permission.[469]

Physical Functioning (Table 104 and Figs 45 and 46). Decreased GFR in NHANES III subjects is associated with impaired walking and lifting ability. In transplant recipients, reduced kidney function is also associated with poorer physical function scores. In one study of patients with decreased GFR, impairment in physical function was not significantly related to the level of kidney function, but physical impairment was 8 times worse than in the general population. Dialysis patients report greater physical dysfunction than transplant recipients and diabetic dialysis and transplant patients are more likely to report physical dysfunction than those patients who do not have diabetes.

Depression (Table 105). Reduced kidney function is associated with poorer psychosocial functioning, higher anxiety, higher distress, decreased sense of well-being, higher depression, and negative health perception. Depressed patients are more likely to report poor life satisfac-

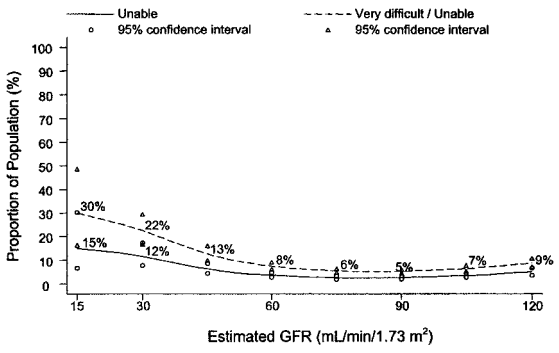


Fig 45. Adjusted prevalence of physical inability to walk by GFR category (NHANES III). Predicted prevalence of physical inability to walk one-quarter mile among adult participants age 20 years and older in NHANES III, 1988 to 1994. Values are adjusted to age 60 years using a polynomial regression. 95% confidence intervals are shown at selected levels of estimated GFR.

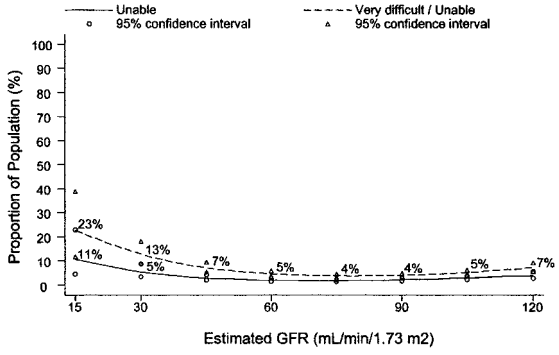


Fig 46. Adjusted prevalence of physical inability to lift by GFR category (NHANES III). Predicted prevalence of physical inability to lift 10 pounds among adult participants age 20 years and older in NHANES III, 1988 to 1994. Values are adjusted to age 60 years using a polynomial regression. 95% confidence intervals are shown at selected levels of estimated GFR.

Table 104. Physical Functioning and Kidney Function

Author, Year	Instrument/ QoL Parameters	No. of Subjects	Applicability	GFR Range (mL/min/1.73 m^2) 0 30 60 90 120	Results*	Quality
Rocco,[469] 1997	QWB: Physical activity, Mobility	900			⬆	●
Korevaar,[470] 2000	SF-36: Physical function EuroQol: Mobility, Self-care	301			⬆	●
Shidler,[471] 1998	KPS: Physical function	50			⬆	●
Klang,[472] 1996	SIP: Physical dimension	38			⬆	●
Harris,[459] 1993	SIP: Physical dimension	360			⇔	○
Fujisawa,[473] 2000	SF-36: Physical function	231		S_{Cr} 1.2 ±0.5 mg/dL	⬆	○
Churchill,[477] 1987	RHIE: Physical function	171		ND	⬆ (transplant vs. dialysis)	○
Manninen,[476] 1991	SIP: Physical dimension, Weight carrying	226		ND	⬆ (transplant vs. dialysis)	○

* ⬆ = higher GFR associated with better physical functioning (statistically significant);
⇔ = GFR *not* associated with level of physical functioning.

Abbreviations: QWB, Quality of Well-Being Scale; SF-36, Medical Outcomes Study Short Form 36; KPS, Karnofsky Performance Scale; SIP, Sickness Impact Profile; RHIE, Rand Health Insurance Experiment instrument

tion, irrespective of kidney function. Dialysis patients report significantly lower "happiness with personal life" and lower psychosocial functioning than transplant recipients. In elderly Mexican Americans, kidney disease has been found to be predictive of depressive symptoms.

Employment and Usual Activities (Table 106). Reduced kidney function is associated with lower employment. In those with chronic kidney disease and GFR <50, the presence of physical dysfunction is significantly related to unemployment, but the association to kidney function is not significant since physical dysfunction is not uniformly present. Full-time employment is higher for those with decreased GFR (mean serum creatinine 5.4 mg/dL, 69%) compared with those with kidney failure (mean serum creatinine 13.7 mg/dL, 12%). More dialysis patients report their health limits work and other activities than those with functioning transplants. Dialysis and transplant patients with diabetes are more likely to report difficulty working than dialysis and transplant patients without diabetes.

Social Functioning (Table 107). Reduced kidney function is associated with reduced social activity, social functioning, and social interaction. Dialysis patients report fewer neighborhood acquaintances, social contacts, and worse social well-being than healthy individuals while transplant recipients report higher social function and social interaction than those on dialysis. Diabetics on dialysis or with transplants are more likely to report problems with social interaction than nondiabetic patients. Level of perceived social support in chronic kidney disease is not associated with the level of kidney function.

LIMITATIONS AND EXCEPTIONS

Most study samples were not randomly selected. Medication usage was not reported even if medications (eg, anti-depressants) could affect outcomes. Seven of 12 studies did not provide full information on patient demographics. Three studies reported differences between groups of very unequal sizes and one reported percentages but did not report whether observed differences were statistically significant.

Table 105. Mental Health, Depression & Well-Being and Kidney Function

Author, Year	Instrument/ QoL Parameters	No. of Subjects	Applic-ability	GFR Range (mL/min/1.73 m^2) 0 30 60 90 120	Results*	Quality
Rocco,[469] 1997	SCL-90R: Psychological distress	936			⬆	●
Korevaar,[470] 2000	SF-36: Mental health EuroQol: Anxiety/Depression	301			⬆	●
Shidler,[471] 1998	BDI: Depression CDI: Depression SWLS: Life satisfaction	50			⇔	●
Klang,[472] 1996	SIP: Psychosocial dimension STAI: Anxiety	38			⬆	●
Harris,[459] 1993	SIP: Psychosocial subscale, Mental & emotional dysfunction	360			⇔	◉
Fujisawa,[473] 2000	SF-36: Mental health, Role emotional	231		S_{cr} 1.2 ±0.5 mg/dL	⇔	◉
Sacks,[475] 1990	BDI: Depression CDI: Depression	73		S_{cr} 5.4 ±3.4 mg/dL	⬆	◉
Black,[476] 1998	CES-D: Depression	2,823 (19[a])		ND	⬆	○
Churchill,[477] 1987	RHIE: Happiness with personal life	171		ND	⬆ (transplant vs. dialysis)	○
Manninen,[476] 1991	SIP: Psychosocial dimension, Emotional behavior	226		ND	⬆ (transplant vs. dialysis)	○

* ⬆ = higher GFR associated with better functioning and well-being (statistically significant);
⇔ = GFR *not* associated with functioning and well-being.

[a] Only 19 subjects had self-reported chronic kidney disease.

Abbreviations: SCL-90R, Symptom Checklist-90R; SF-36, Medical Outcomes Study Short Form 36; BDI, Beck Depression Inventory; CDI, Cognitive Depression Index; SWLS, Satisfaction with Life Scale; SIP, Sickness Impact Profile; CES-D, Center for Epidemiological Studies Depression Scale; RHIE, Rand Health Insurance Experiment instrument

Historically, there has been no "gold standard" definition for quality of life or functioning and well-being. Researchers have studied multiple variables using standardized and non-standardized instruments. Thus, results are not comparable to one another.[479] With lack of instrument comparability, findings appear to be conflicting. Many studies have examined the relationships between functioning and well-being and treatment modalities after the onset of kidney failure. Few studies of persons with decreased GFR have examined the relationship between level of GFR and functioning and well-being. Three of the studies of individuals with decreased GFR had such severely restrictive inclusion criteria for level of kidney function that functioning and well-being deficits were already present. Of the 12 studies reported, 3 reported no measure of kidney function and 2 reported only serum creatinine, a less reliable measure of kidney function than GFR or creatinine clearance. Most of the studies reported only mean values for kidney function. Only the MDRD Study and NHANES III examined functioning and well-being at a wide range of levels of kidney function. Precise statements about how early deficits in domains of functioning and well-being occur as kidney function deteriorates require this essential data. Finally, since anemia has been shown to limit functioning and well-being, inadequate anemia management in studies conducted prior to the widespread use of erythropoietin could have affected outcomes. Therefore, recent functioning and well-being outcomes may not be comparable

Table 106. Employment, Home Management, Recreation & Pastimes and Kidney Function

Author, Year	Instrument/ QoL Parameters	No. of Subjects	Applicability	GFR Range (mL/min/1.73 m²) 0 30 60 90 120	Results*	Quality
Korevaar,[470] 2000	SF-36: Role physical, Role emotional EuroQol: Usual activities	301	↑↑		↑	●
Shidler,[471] 1998	KPS: Functional status	50	↑↑		↑	●
Klang,[472] 1996	SIP: Work, Home management	38	↑↑		↑	●
Harris,[459] 1993	SIP: Unemployment	360	↑↑		⇔	◎
Fujisawa,[473] 2000	SF-36: Role physical, Role emotional	231	↑↑	S_{Cr} 1.2 ±0.5 mg/dL	⇔	◎
Sacks,[475] 1990	SAS-SR: Role disruption, Employment	73	↑↑	S_{Cr} 5.4 ±3.4 mg/dL	↑	◎
Churchill,[477] 1987	RHIE: Heavy work	171	↑↑	ND	↑ (transplant vs. dialysis)	○
Manninen,[476] 1991	SIP: Work ability, Seeing to read, inspect	226	↑	ND	↑ (transplant vs. dialysis)	○

* ↑ = higher GFR associated with better functioning and well-being (statistically significant);
⇔ = GFR *not* associated with functioning and well-being.

Abbreviations: SF-36, Medical Outcomes Study Short Form 36; KPS, Karofsky Performance Scale; SIP, Sickness Impact Profile; SAS-SR, Social Adjustment Scale Self-Report; RHIE, Rand Health Insurance Experiment instrument

to outcomes reported in studies prior to 1989 even if the same instruments were used.

CLINICAL APPLICATIONS

The conferees at the Institute of Medicine (IOM) Workshop "Assessing Health and Quality of Life Outcomes in Dialysis" recommended that ESRD providers:

- Assess functioning and well-being in kidney disease using standardized survey instruments that are valid, reliable, responsive to changes, easily interpretable, and easy to use, such as the Dartmouth COOP Charts, the Duke Health Profile/Duke Severity of Illness (DUKE/DUSOI), Medical Outcomes Study 36-Item Short Form (SF-36), or the Kidney Disease Quality of Life (KDQOL).
- Assess patient functioning and well-being early in chronic kidney disease to establish a baseline, to maintain or improve health status, and to manage the disease continuum by linking clinical and health outcomes with functional status outcomes.[454]

Data reported in the reviewed studies suggest that decreased kidney function affects patients' functioning and well-being through several dimensions. Deficits in functioning are reported by patients even at early stages of chronic kidney disease, and persist even after transplantation. The implications of these findings are:

- Clinicians should assess functional status and well-being as soon as possible after referral in order to obtain baseline data and enable early intervention to improve functioning and well-being.
- Clinicians should regularly reassess functioning and well-being to ascertain the patient's current status and the effectiveness of interventions to improve functioning and well-being. Reassessment is needed when a patient reports increased

Table 107. Social Functioning and Kidney Function

Author, Year	Instrument/ QoL Parameters	No. of Subjects	Applicability	GFR Range (mL/min/1.73 m²) 0 30 60 90 120	Results*	Quality
Rocco,[469] 1997	QWB: Social activity	900			⬆	●
Korevaar,[470] 2000	SF-36: Social function EuroQol: Usual activities	301			⬆	●
Shidler,[471] 1998	MSP: Social support	50			⇔	●
Klang,[472] 1996	SIP: Social interaction	38			⬆	●
Fujisawa,[473] 2000	SF-36: Social functioning, Role emotional	231		S_{Cr} 1.2 ±0.5 mg/dL	⬆	◎
Sacks,[475] 1990	SAS-SR: Social & leisure activities	73		S_{Cr} 5.4 ±3.4 mg/dL	⇔	◎
Churchill,[477] 1987	RHIE: Social contacts, Group participation, Social well being, Neighborhood acquaintance	171		ND	⬆ (transplant vs. dialysis)	○
Manninen,[476] 1991	SIP: Work ability, Seeing to read, inspect	226		ND	⬆ (transplant vs. dialysis)	○

* ⬆ = higher GFR associated with better functioning and well-being (statistically significant);
⇔ = GFR *not* associated with level of functioning and well-being.

Abbreviations: QWB, Quality of Well-Being Scale; SF-36, Medical Outcomes Study Short Form 36; MSP, Multidimensional Scale of Perceived Social Support; SIP, Sickness Impact Profile; SAS-SR, Social Adjustment Scale Self-Report; RHIE, Rand Health Insurance Experiment instrument

frequency or severity of symptoms, has a new complication of kidney disease, has an access for dialysis placed, starts dialysis, changes modality, or participates in a clinical or rehabilitation intervention (eg, counseling, peer support, education, physical therapy or independent exercise, or vocational rehabilitation).

These recommendations are based on the opinions expressed by the authors of most of the studies reviewed for this guideline, as well as those of recognized experts in functioning and health status outcomes measurement who attended the IOM Workshop.

IMPLEMENTATION ISSUES

Researchers may use any of a wide array of instruments to measure functioning and well-being throughout the course of chronic kidney disease. However, clinicians want to know what instrument to use, when to use it, and who should administer, score, and analyze the data. In general, it is practical for clinicians to use only a few instruments and to gain experience with them. Based on the literature reviewed for this guideline, it appears that any clinician treating patients with decreased GFR can administer the Dartmouth COOP Charts, DUKE Health Profiles, Kidney Disease Quality of Life, or SF-36 that have been used with dialysis and transplant patients (Table 108). In the clinical setting ease of use is essential. These surveys are recommended because each has an instructional manual and patients can complete them independently or with limited assistance. To assess specific limitations in functioning and well-being, clinicians can supplement these general instruments with more specific instruments including performance-based tests of physical functioning.

Table 108. Functioning and Well-Being Measures

Instrument (Applications)	Specifications	Ordering Information
Dartmouth COOP Functional Health Assessment Charts (Generic for youth, adult and elderly; one for dialysis)	Time: <10 min (youth & adult), 20 min. (elderly & dialysis) Domains: physical, emotional, daily activities, social activities, social support, pain, overall health quality of life, financial, diseases, symptoms/problems, burden of dialysis Cost: depends on choice of scoring Scoring/Analysis: several options Languages: unknown Version for Visually Impaired: large print, pictures	FNX Corporation 1 Dorset Lane Lebanon, NH 03766 (800) 369-6669 Attn: John Wasson, MD Web: *http://home.fnxnet.com*
Duke Health Profile (DUKE) (Generic)	Time: 5 min. Domains (generic): physical health, mental health, social health, general health, perceived health, self-esteem, anxiety, depression, anxiety-depression, pain, disability Cost: free for non-commercial use; manual $30 Automated version: Duke University Medical Center Languages: 19 Scoring/analysis: Duke University Medical Center Version for Visually Impaired: no	George R. Parkerson, Jr., MD Department of Community & Family Medicine Duke University Medical Center Box 3886 Durham NC 27710 (919) 681-6560 Email: *george.parkerson@duke.edu* Web: *www.qlmed.org/duke/*
Kidney Disease Quality of Life (KDQOL™) (Kidney-specific)	Time: 30 min. (long form) 16 min. (short form) Domains (generic): physical functioning, role limitations-physical, bodily pain, general health, vitality, social functioning, role limitations-emotional, mental health (ESRD/dialysis): symptoms/problems, effects of kidney disease on daily life, burden of kidney disease, cognitive function, work status, sexual function, quality of social interaction, sleep Cost: free single, can make unlimited copies Automated version: HDO at (770) 889-5558 Scoring/analysis: HDO at (770) 889-5558 Languages: multiple Version for visually impaired: large print	RAND Corp. 1333 H St., NW Washington, DC 20004-4792 Attn: Caren Kamberg E-mail: *caren_kamberg@rand.org* Web: *www.qlmed.org/KDQOL/index.html*
Medical Outcomes Study 36 Item Short Form (SF-36[a]) (Generic)	Time: 12-15 min. Domains (generic): physical functioning, role limitations-physical, bodily pain, general health, vitality, social functioning, role limitations-emotional, mental health Cost: free, copy with permission Scoring/analysis: Quality Metric, Inc. (401) 334-8800 Languages: multiple Version for visually impaired: unknown	QualityMetric Inc. 640 George Washington Hwy Ste 201 Lincoln, RI 02865 (888) 947-9800) Email: info@qmetric.com Web: *www.qlmed.org/SF-36/index.html* or *http://sf-36.com/*

[a] Shorter versions include the SF-12 and SF-8.

RESEARCH RECOMMENDATIONS

Research in dialysis patients has shown that functioning and well-being pre-treatment may predict post-treatment outcomes. Therefore, large-scale longitudinal studies are needed to evaluate the relationship between GFR and all domains of functional status and well-being throughout the course of progression of kidney disease. More research should be undertaken using the recommended standardized instruments and their outcomes compared. Whenever specific medications could affect outcomes, usage should be assessed. Because conditions such as anemia, bone disease, cardiovascular, disease, and diabetes can affect functioning and well-being, researchers need to study whether appropriate management of these conditions improves functioning and well-being. Finally, researchers need to examine the effectiveness of rehabilitation interventions in earlier stages of chronic kidney disease. Doing so could provide further scientific evidence for the relationship of kidney function and treatment on patients' risk of dysfunction, hospitalization, and death and increase understanding of what interventions improve functioning and well-being and reduce the burden of chronic kidney disease on the patient, his or her family, and society.