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Nutritional Management of the Chronic Kidney Disease Patient

By LeeAnn Smith, MPH, RD. *LeeAnn is a renal dietitian for Crescent Heights Dialysis Center in Los Angeles, California. She can be reached at leeann.smith@davita.com*

Introduction

An estimated nineteen million (11%) adults in the United States have chronic kidney disease (CKD) (1). Both CKD and acute renal failure (ARF) are common illnesses treated in the hospital setting. This article will summarize the nutritional goals and interventions throughout the spectrum of kidney disease including CKD Stages 1 - 5, renal transplantation, and ARF. The role of nutrition in nephrology should not be underestimated. The nutrition prescription, which must be continually altered during the progression of CKD, is an essential component in the overall treatment plan. In addition, nutritional status plays a significant role in the well-being and survival of these patients. Kidney disease, from etiology to treatment, is a very complicated illness which requires a multi discipline team approach to manage. The following provides practical and scientific reasoning for the nutritional care of these patients.

Chronic Kidney Disease: Stages 1 to 4

Nutrition goals in chronic kidney disease include decreasing the accumulation of nitrogenous wastes, prevention of malnutrition and delaying the progression of kidney disease (2). One criterion defining CKD is kidney damage for three months or greater, characterized by structural or functional renal abnormalities, presenting with either pathological abnormalities or irregular blood, urine or imaging study results, which may or may not be associated with a decreased Glomerular Filtration Rate (GFR) (3). A second criterion of CKD is a GFR less than 60 mL/min/1.73m² that is present for three months or greater, irrespective of the presence of renal damage (3). As GFR declines, the severity of associated complications increases. The use of both low protein diets (LPD) and very low protein diets (VLPD) supplemented with essential amino acids (EAA) and/or ketoacids (KA) has been evaluated in the treatment to delay the progression of CKD.

Patients with CKD, not undergoing dialysis, may be managed with a low protein, low phosphorus diet to prevent or treat uremic symptoms and to delay the progression of the disease (4, 5, 6). Elevations in serum phosphorus and potassium noted in early stages CKD suggest that dietary modification of these nutrients may be necessary (7). Protein restrictions may be used in patients with CKD that have a) symptoms of uremia, b) edema or poorly controlled hypertension c) continued decline in kidney function despite blood pressure control and use of angiotensin converting enzyme inhibitors (2). There is evidence that a protein- sparing mechanism occurs when dietary protein intake is reduced allowing for a sustained favorable metabolic response to decreased protein intakes in patients with CKD (8).

Nutritional Adequacy of Protein Restriction

Various studies have evaluated the nutritional adequacy of LPD and VLPD in patients with mild to severe CKD, predialysis. Patients receiving a LPD

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(0.6 g/kg/day of protein) or a VLPD (0.3 g/kg/day of protein) supplemented with EAA and/or KA experienced no signs of severe malnutrition (9, 10). Furthermore, a reduction in serum urea nitrogen is attained with the VLPD and KA (10). A study of diet in mild CKD providing >31 kcal/kg/day and 0.7 g/kg/day of protein was considered "metabolically and nutritionally safe" (8). K/DOQI guidelines indicate a LPD allowing 0.60 g/kg/day of protein and 35 kcal/kg/day (<60 years of age) and 30-35 kcal/kg/day (≥60 years of age) in CKD with a GFR <25 mL/min without dialysis (3). However, modification of dietary protein in these patients is appropriate only when energy consumption is adequate (3).

Delay of Chronic Kidney Disease Progression

To evaluate the potential delay of initiation of dialysis on a VLPD, 0.3 g/kg of ideal body weight (IBW)/day and 35 kcal/kg IBW/day plus supplemented EAA and/or KA was administered (5). Renal survival on nutritional therapy was calculated as the time from when the GFR became 10 ml/min (15 ml/min in patients with diabetes) to the date of dialysis initiation. Median renal survival was 353 days and there was no significant change in albumin levels or experience of malnutrition. Mortality during the first two years of dialysis was well below the national average (5). This suggests that a very low protein diet, supplemented with EAA and/or KA is nutritionally safe and may delay the necessity of dialysis initiation. However, further study of this diet with larger numbers of patients is necessary.

Current studies indicate a favorable role for LPD in mild to severe CKD, stages 3 and 4, in delaying the progression of renal disease while maintaining nutritional status. Further research is needed regarding the amount and type of protein required and safety of length of time on the diet. Also, it is important to note that very low protein diets are supplemented with EAA or KA to maintain nutritional adequacy and prevent protein malnutrition. A metabolic response to decreased protein intakes in patients with CKD may be present, resulting in a nitrogen-sparing effect. Individualized nutrition counseling with a renal dietitian, who possesses expertise in renal nutrition principles, is imperative to achieving compliance with the predialysis nutrition prescription and insuring nutritional adequacy.

Nephrotic Syndrome

Nephrotic syndrome, characterized by high levels of urinary protein loss (≥3g proteinura/day) and urinary albumin loss (microalbuminuria), affects large numbers of patients (11). Microalbuminuria in both diabetes and hypertension predicts progression of kidney disease and cardiovascular risk (11). Both the type and amount of dietary protein consumed has an effect on urinary albumin excretion in patients with diabetes.

Although high biological value protein is usually recommended, vegetarian diets containing soy and plant-based protein may reduce urinary protein loss, improve serum protein levels, ameliorate the progression of diabetic nephropathy, and prevent obesity-related renal diseases (11). A vegetarian diet consisting of 0.7 g/kg/day of protein and 33 to 35 kcal/kg/day in the early stages of CKD and 0.3 g/kg/day of protein and 30 to 35 kcal/kg/day once creatinine clearance is <20ml/min has been shown to delay the progression of CKD in patients with diabetic nephropathy (12). As mentioned previously, EAA and KA supplements are necessary in the very low protein diet to avoid protein malnutrition. Patients experienced decreases in urinary protein losses and fasting blood glucose levels (12).

A LPD of 0.45 to 0.80 g/kg/day of protein and 35 kcal/kg/day is considered safe for patients with nephrotic syndrome without catabolic illnesses, not receiving catabolic medications and without severe proteinuria (>15 g/day) (11). Furthermore, 0.8 g/kg/day of protein plus 1 g protein per gram urinary protein loss and 35 kcal/kg/day maintains nitrogen balance in nephrotic patients (13). It should be emphasized that adequate calories must be given to prevent the loss of lean muscle mass. A low sodium (<2 g sodium), reduced fat diet containing 0.8 to 1.0 g protein/kg/day and 35 kcal/kg/day is currently recommended for patients with nephrotic syndrome (11).

Chronic Kidney Disease: Stage 5

CKD Stage 5 is indicated by either a GFR <15 mL/min/1.73 m², which is often associated with uremia, or the necessity to initiate renal replacement therapy (dialysis or transplantation) (3). This section discusses the nutrition

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issues of patients with kidney failure undergoing dialysis. Multiple factors contribute to compromised nutritional status and protein depletion in patients with kidney failure. Protein energy malnutrition (PEM) is common among patients with kidney failure and is associated with increased morbidity and mortality, including cardiovascular-related fatality (14, 15). The renal dietitian, along with the nephrology team, takes steps to prevent malnutrition, identify potential causes of malnourishment and devise nutritional interventions to improve patient outcomes.

There are two distinct forms of malnutrition in this patient population. The first type is compared with "classic" malnutrition associated with inadequate dietary consumption, a decrease in lean body mass and usually a normal serum albumin level. The second form is related to inflammation and atherosclerosis, resulting in decreased serum albumin despite adequate dietary intake (16). Low body mass index (BMI) is associated with decreased survival in kidney failure (17). Two significant factors predisposing patients undergoing dialysis to loss of lean body mass include dialysate amino acid, protein and glucose losses and anorexia (16).

Patients undergoing hemodialysis (HD) and peritoneal dialysis (PD) may lose 2-8 g and 5-12 g of free amino acids per treatment day, respectively (16). These losses are more profound when coupled with poor appetite and dietary intake. Among the 300,000 individuals with CKD Stage 5 on dialysis, it is suggested that approximately 70% may consume less than recommended amounts of calories and protein (17,18). Causes of poor appetite among individuals with kidney failure include underdialysis, comorbid conditions, use of multiple medications, and psychosocial issues, should be considered when intervening to improve the nutritional status of patients (16).

Malnutrition-Inflammation Complex Syndrome

There is a mounting body of literature and discussion surrounding the phenomenon known as malnutrition-inflammation complex syndrome (MICS). This term is used to describe the relationship between PEM and cardiovascular disease in patients on dialysis, both common and coexisting conditions in this population, which are related through inflammation. MICS is associated with hypoalbuminemia, suboptimal appetite, hypercatabolism, poor dialysis outcomes, and decreased quality of life (19, 20, 21, 22).

Markers of MICS include proinflammatory cytokines such as interleukin-1, interleukin-6 and tumor necrosis factor-a; serum negative acute phase proteins albumin and prealbumin; and C-reactive protein, total iron binding capacity, creatinine, total cholesterol and normalized protein nitrogen appearance (22, 23). These are common correlates of mortality in patients undergoing hemodialysis (19).

Both calorie and protein recommendations are greater for patients with CKD Stage 5 undergoing dialysis compared to the recommendations for patients with CKD Stages 2 - 4. Patients on dialysis have significantly higher resting energy expenditure (REE) than predialysis patients (24). Potential factors contributing to increased REE in kidney failure include severe secondary hyperparathyroidism and

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Table I. Causes of Protein Catabolism in Patient with ARF (22, 32)

Uremic Toxins (ureagenesis)
- ↑ hepatic glucose production in animal studies

Altered Carbohydrate and Protein Metabolism
- ↓ protein synthesis, ↑ protein breakdown and ↑amino acid uptake ↓ activity of adenosine triphosphate and ubiquitin-dependent proteolytic pathway

Hormone and Immune Responses
- Insulin resistance
- Increased secretion of catabolic hormones (catecholamine, glucagon, growth hormone, and glucocorticoids)
- Secretion of proinflammatory cytokines, acute phase reaction (tumor necrosis factor, interleukin-6 and interleukin-1)
- Hyperparathyroidism

Metabolic Acidosis

Inadequate Nutritional Intake

Renal Replacement Therapy
- Loss of nutritional substrates
- Activation of protein catabolism

the hemodialysis treatment (25, 26). While it is indicated that inflammation is correlated with an increase in REE in CKD, additional studies are needed to investigate the role of inflammation on resting energy expenditure in patients on renal replacement therapy (27).

Nutrition Recommendations for CKD Stage 5

Protein recommendations are 1.2 to 1.4 g/kg/day for hemodialysis patients and up to 1.5 g/kg/day for PD patients. It is suggested that greater than 50% of protein should be of high biological value (16). Energy requirements should be generous to allow for utilization of dietary protein in healing and tissue repair and must be individualized to account for activity level and nutritional goals. Approximately 30 to 35 kcal/kg/day is suggested on hemodialysis and 25 to 30 kcal/kg/day on PD (16). To account for substantial energy absorption in the form of glucose through dialysate (approximately 680 kcal/day) on PD, dietary energy requirements are slightly less than what is recommended on HD (16).

Renal Transplantation

Patients with functioning kidney transplants typically have fewer dietary restrictions that are common with patients with CKD Stages 2-5, however, nutrition continues to play a vital role in the health and survival of these patients. When advising renal transplantation patients and candidates, nutrition objectives include mitigating the potential side effects of immunosuppressive therapy, addressing previously existing nutrition-related conditions, and maintaining optimal function of the kidney.

The adverse effects of glucocorticoid immunosuppressive therapy on the nutritional and metabolic status of patients living with renal transplants are numerous and include protein catabolism, obesity, hyperlipidemia, and glucose intolerance (28). Insulin resistance caused by steroid therapy further complicates the care of patient with diabetes (28). In addition, a portion of patients receiving kidney transplants without diabetes will develop the illness within the first three weeks after surgery (29). These metabolic alterations and nutritional consequences must be considered when providing diet counseling to kidney transplant recipients.

Both very low and very high BMI is adversely correlated with patient and kidney transplant survival (30). This suggests that maintaining a healthy weight is imperative for patients with a kidney transplant.

Use of high protein, low carbohydrate diets have proved successful in preventing cushinoid features and improving nitrogen balance in renal transplant patients receiving steroid therapy (31). However there is insufficient data evaluating the safety and efficacy of this type of diet in recipients of kidney transplants. When considering protein needs of these patients, equilibrium must be achieved between providing sufficient protein for wound healing, treating pre-existing protein deficiency, and improving nitrogen balance while minimizing the accumulation of waste products.

Nutrition Recommendations in Renal Transplantation

The first month after renal transplant 1.3 to 1.5 g/kg/day of protein and 30 to 35 kcal/kg/day is recommended (28). After one month post-transplant 1.0 g/kg/day of protein and adequate calories to achieve and maintain ideal weight is suggested. It is important that patients receiving kidney transplants receive comprehensive nutrition therapy not only to prepare for surgery, but to transition into a new stage of kidney disease.

Acute Renal Failure

Risk of mortality in patients with acute renal failure is correlated with nutritional and metabolic factors (32). Goals of nutrition therapy in ARF include the prevention of malnutrition and the preservation of lean body mass. An appropriate nutrition plan, which considers the presence and severity of catabolism and the type and intensity of renal replacement therapy, while addressing both the underlying illness and resulting complications, must be developed to meet the unique needs of the patient.

Often ARF is associated with sepsis, trauma and multi-organ failure resulting in a hypercatabolic state with complex hormonal and metabolic alterations such as insulin resistance, hypertriglyceridemia and hepatic gluconeogenesis (32, 33, 34, 35). A major metabolic alteration in ARF, protein catabolism, characterized by the release of amino acids and a negative nitrogen balance is a result of numerous factors present in these critically ill patients (see Table I). Therefore, nutritional requirements in ARF

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are influenced by a multitude of potential complications in addition to the underlying disease. When delivering nutrition support to these patients, meeting the minimum nutritional requirements for chronic kidney disease is inadequate.

Nutrition Recommendations and Severity of ARF

Acute renal failure may be categorized into three groups related to nutrition needs and the severity of ARF. Group I usually consists of patients that are often well nourished and able to feed orally. Often the cause of ARF is due to nephrotoxins such as therapeutic drugs, radiocontrast agents, carcinogens, metals, abused drugs, and industrial chemicals (36). These patients may be given 0.6 g/kg/day of protein initially and gradually increased to 0.8 g/kg/day with a caloric provision of 25 kcal/kg/day (32). When undergoing hemodialysis or peritoneal dialysis, this amount of protein should be increased to 1.0 to1.2 g/kg/day and 1.4 d/kg/day, respectively to compensate for amino acid and protein losses (32).

Patients in group II may be moderately hypercatabolic and suffering from infections or injury. Enteral feedings, parenteral nutrition or both may be necessary forms of nutrition support. These patients will require approximately 0.8 to 1.2 g/kg/day of protein and 20 to 30 kcal/kg/day (32).

Group III includes patients with severe infection, major trauma and burns presenting in a severe hypercatabolic state. Patients with ARF and sepsis have a 68% rate of mortality (37). Patients in Group III should receive 1.2 to 1.5 g/kg/day of protein (or amino acids) and when undergoing renal replacement therapy, protein intake should reach 1.5 g/kg/day (32). Energy requirements are 25 to 35 kcal/kg/day.

Medical Nutrition Support in ARF

Enteral nutrition is considered the standard method of nutrition support in critically ill patients, including those with ARF. Though enteral feeding is considered safe and effective in patients with ARF, it may be impossible to utilize this route exclusively to meet nutrition needs (38, 39). It may be necessary to supplement enteral nutrition with parenteral nutrition or total parenteral nutrition (TPN) may be necessary.

One study of critically ill patients on continuous renal replacement therapy for ARF concluded that increased nitrogen balance, achieved with high doses of protein (>2 g/kg/day), improved probability of survival (40). High protein (1.5-1.8 g/kg/d) and relatively low calorie (25-35 kcal/kg/d) dietary regimens may improve nitrogen balance (41). One study of patients receiving both TPN and renal replacement therapy found that on a nitrogen intake of 0.25 g/kg/day, higher caloric provision (40 kcal/kg/day) did not improve nitrogen balance compared with a lower caloric intake (30 kcal/kg/day) (42). This suggests that nutrition support in severe cases of ARF should provide high doses of protein and sufficient calories to improve nitrogen balance, which leads to increased likelihood of survival.

Additional research on the nutritional management of CKD is needed to ensure the best care and quality of life for patients. As focus shifts to identifying patients with CKD early, it will be imperative to understand the role that nutrition plays in delaying the progression of CKD in much greater detail.

References

1. Coresh J, Aslor BC, Greene T, Eknoyan G, Levey AS. Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third National Health and Nutrition Examination Survey. *Am J Kidney Dis.* 2003;41:1-12.
2. Mandayam S & Mitch WE. Requirements for protein, calories, and fat in the predialysis patient. In: Mitch WE & Khahr S. *Handbook of Nutrition and the Kidney.* Philadelphia, PA: Lippincott Williams & Wilkins, 2002; 115-137.
3. National Kidney Foundation. K/DOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification, and Stratification. *Am J Kidney Dis. 2002; 39(2 Supp 1): S1-266.*
4. Walser M, Mitch WE, Maroni BJ, Kopple JD. Should protein intake be restricted in predialysis patients? *Kidney Int.* 1999;55:771-777.
5. Walser M & Hill S. Can renal replacement be deffered by a supplemented very low protein diet? *J Am Soc Nephrol*. 1999;10:110-116.
6. Aparicio M, Chauveau P, De Précigout V, Bouchet JL, Lasseur C, Combe C. Nutrition and outcome on renal

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replacement therapy of patients with chronic renal failure treated by supplemented very low protein diet. *J Am Soc Nephrol.* 2000;11:708-716.

7. Hsu C & Chertow GM. Elevations of serum phosphorus and potassium in mild to moderate chronic renal insufficiency. *Nephrol Dial Transplant.* 2002;17:1419-1425.
8. Bernhard J, Beaufrère B, Laville M, Fouque D. Adaptive response to a low- protein diet in predialysis chronic renal failure patients. *J Am Soc Nephrol.* 2001;12: 1249-1254.
9. Cupisti A, DíAlessandro C, Morelli E, Rizza GM, Galetta F, Franzoni F, Barsotti G. Nutritional status and dietary manipulation in predialysis chronic renal failure patients. *J Renal Nutr.* 2004;14:127-133.
10. Feiten SF, Draibe SA, Watanabe R, Duenhas MR, Baxmann AC, Nerbass FB, Cuppari L. Short-term effects of a very-low-protein diet supplemented with ketoacids in nondialyzed chronic kidney disease patients. *Eur J Clin Nutr.* 2005;59:129-136.
11. Yeun JY & Kaysen GA. Nephrotic syndrome: nutritional consequences and dietary management. In: Mitch WE & Khahr S. *Handbook of Nutrition and the Kidney.* Philadelphia, PA: Lippincott Williams & Wilkins, 2002; 160-170.
12. Barsotti G, Cupisti A, Barsotti M, Sposini S, Palmieri D, Meola M, Lenti C, Morelli E. Dietary treatment of diabetic nephropathy with chronic renal failure. *Nephrol Dial Trans.* 1998;13:49-52.
13. Maroni BJ, Staffeld C, Young VR, Manatunga A, Tom K. Mechanisms to achieve nitrogen equilibrium with a protein- restricted diet. *J Clin Invest.* 1997;99:2479-2487.
14. Kopple JD. Nutritional status as a predictor of morbidity and mortality in maintenance dialysis patients. *ASAIO J.* 1997;43:246-250.
15. Fung F, Sherrard DJ, Gillen DL, Wong C, Kestenbaum B, Seliger S, Ball A, Stehman-Breen C. Increased risk for cardiovascular mortality among malnourished end-stage renal disease patients. *Am J Kidney Dis.* 2002; 40:307-314.
16. Boxall MC & Goodship T. Nutritional requirements in hemodialysis. In: Mitch WE & Khahr S. *Handbook of Nutrition and the Kidney.* Philadelphia, PA: Lippincott Williams & Wilkins, 2002;218-225,234.
17. United States Renal Data System: US Department of Public Health and Human Services, Public Health Service, National Institutes of Health, Bethesda, MD 2002.
18. Bossola M, Muscaritoli M, Tazza L, Panocchia N, Liberatori M, Giungi S, Tortorelli A, Fanelli FR, Luciani G. Variables associated with reduced dietary intake in hemodialysis patients. *J Ren Nutr.* 2005;15:244-252.
19. Colman S, Bross R, Benner D, Chow J, Braglia A, Arzaghi J, Dennis J, Martinez L, Baldo D, Agarwal V, Trundnowski T, Zitterkoph J, Martinez B, Khawar O, Kalantar-Zadeh K. The nutritional and inflammatory evaluation in dialysis patients (NIED) study: overview of the NIED study and the role of dietitians. *J Ren Nutr.* 2005;15:231-243.
20. Kalantar-Zadeh K, Block G, Humphreys MH, Kopple JD. Reverse epidemiology of cardiovascular risk factors in maintenance dialysis patients. *Kidney Int.* 2003;63: 793-808.
21. Kalantar-Zadeh K, Ikizler TA, Block G, Avram MM, Kopple JD. Malnutrition-inflammation complex syndrome in dialysis patients: causes and consequences. *Am J Kidney Dis.* 2003;42:864-881.
22. Kopple JD & Massry SG. *Nutritional Management of Renal Disease.* 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2002;4-5,193.
23. Kalantar-Zadeh K, Kopple JD, Humphreys MH, Block G. Comparing outcome predictability of markers of malnutrition-inflammation complex syndrome in haemodialysis patients. *Nephrol Dial Transplant.* 2004; 19:1507-1519.
24. Neyra R, Chen KY, Sun M, Shyr Y, Hakim RM, Ikizler TA. Increased resting energy expenditure in patients with end-stage renal disease. *J Parenter Enteral Nutr.* 2003;27:36-42.
25. Cuppari L, Barbosa De Carvalho A, Avesani CM, Kamimura MA, Ribeiro Dos Santos Lobão R, Draibe SA. Increased resting energy expenditure in hemodialysis patients with severe hyperparathyroidism. *J Am Soc Nephrol.* 2004;15:2933-2939.
26. Ikizler TA, Wingard RL, Sun M, Harvell J, Parker RA, Hakim RM. Increased energy expenditure in hemodialysis patients [abstract]. *J Am Soc Nephrol.* 1996;7:2646-2653.
27. Utaka S, Avesani CM, Draibe SA, Kamimura MA, Andreoni S, Cuppari L. Inflammation is associated with

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increased energy expenditure in patients with chronic kidney disease. *Am J Clin Nutr.* 2005;82:801-805.

28. Bertolatus JA. Nutritional requirements of renal transplant patients. In: Mitch WE & Khahr S. *Handbook of Nutrition and the Kidney.* Philadelphia, PA: Lippincott Williams & Wilkins, 2002;95-114.
29. Friedman AN, Miskulin DC, Rosenberg IH, Levey AS. Demographics and trends in overweight and obesity in patients at the time of kidney transplantation. *Am J Kidney Dis.* 2003;41:480-487.
30. Meier-Kriesche HU, Arndorfer JA, Kaplan B. The impact of body mass index on renal transplant outcomes: a significant risk factor for graft failure and patient death. Transplantation. 2002;73:70-74.
31. Whittier FC, Evans DH, Dutton S, Ross G, Luger A, Nolph KD, Bauer JH, Brooks CS, Moore H. Nutrition in renal transplantation. *Am J Kidney Dis.* 1985;6:405-411.
32. Druml W. Nutritional support in acute renal failure. In: Mitch WE & Khahr S. *Handbook of Nutrition and the Kidney.* Philadelphia, PA: Lippincott Williams & Wilkins, 2002;95-113.
33. Levy EM, Viscoli CM, Horwitz RI. The effect of acute renal failure on mortality. A cohort analysis. *JAMA.* 1996;275:1489-1495.
34. Chertow GM, Lazarus JM, Paganini EP, Allgren RL, Lafayette RA, Sayegh MH. Predictors of mortality and the provision of dialysis in patients with acute tubular necrosis. The Auriculin Anaritide Acute Renal failure Study Group. *J Am Soc Nephrol.* 1998;9:692-698.
35. Brivet FG, Kleinknecht DJ, Loirat P, Landais PJ. Acute renal failure in intensive care units- causes, outcome, and prognostic factors of hospital mortality: a prospective, multicenter study. French Study Group on Acute renal failure. *Crit Care Med.* 1996;24:192-198.
36. Kovacic P, Sacman A, Wu-Weis M. Nephrotoxins: widespread role of oxidative stress and electron transfer. *Curr Med Chem.* 2002;9:823-847.
37. Schroeder TH, Hansen H, Dinkelaker K, Kruegar WA, Nohe B, Fretschner R, Unertl K. Influence of underlying disease on the outcome of critically ill patients with acute renal failure. *Eur J Anaesthesiol.* 2004;21:848-853.
38. Metnitz PG, Krenn CG, Steltzer H, Lang T, Ploder J, Lenz K, Le Gall JR, Druml W. Effects of acute renal failure requiring renal replacement therapy on outcome in critically ill patients. *Crit Care Med.* 2002;30:2051-2058.
39. Fiaccadori E, Maggiore U, Giacosa R, Rotelli C, Picetti E, Saripanti S, Melfa L, Meschi T, Borghi L, Cabassi A. Enteral nutrition in patients with acute renal failure. *Kidney Int.* 2004;65:999-1008.
40. Scheinkestel CD, Kar L, Marshall K, Bailey M, Davies A, Nyulas I, Tuxen DV. Prospective randomized trial to assess caloric and protein needs of critically ill, anuric, ventilated patients requiring continuous renal replacement therapy. *Nutrition.* 2003;19:909-916.
41. Macias WL, Alaka KJ, Murphy MH, Miller ME, Clark WR, Mueller BA. Impact of the nutritional regimen on protein catabolism and nitrogen balance in patients with acute renal failure. *J Parenter Enteral Nutr.* 1996; 20:56-62.
42. Fiaccadori E, Maggiore U, Rotelli C, Giacosa R, Picetti E, Parenti E, Meschi T, Borghi L, Tagliavini D, Cabassi A. Effects of different energy intakes on nitrogen balance in patients with acute renal failure: a pilot study. *Nephrol Dial Trans.* 2005;20:1976-1980.