Advances in Practice

Impact of Infection and the Immune Response on Nutritional Status in Patients with Chronic Kidney Disease Undergoing Maintenance Dialysis Therapy

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Patients with chronic kidney disease (CKD) undergoing maintenance dialysis therapy have a lower immune response than healthy subjects, and this increases their susceptibility to infection (1,2). Information from the United States Renal Data System (USRDS) indicates that infection accounts for approximately 12% of deaths in patients undergoing hemodialysis (HD) and 15% of deaths in patients undergoing peritoneal dialysis (PD) in the United States (3).

The majority of deaths attributed to infection in maintenance dialysis patients result from sepsis. Bacterial sepsis (bacteremia) is the second leading cause of death in HD patients (4,5). Bacteremia may lead to the development of infective endocarditis, which affects the endocardium and heart valves, and has a one-year mortality rate of approximately 50% in patients receiving HD therapy (6,7).

Infection may directly affect nutritional status of maintenance dialysis patients by contributing to loss of appetite and development of malnutrition (8). Findings from a recent study of vascular access infections in patients undergoing maintenance HD indicate that a low pre-infection level of serum albumin – one of a panel of nutritional markers in patients with CKD – is associated with increased risk of access infection (9). There is also evidence to suggest that improving nutritional status may decrease the incidence of sepsis (4).

An understanding of the relationship among infection, the immune response and nutritional status might enhance the ability of the renal dietetics professional to provide effective intervention for their patients with CKD. This article will provide an overview of immune system components, examine the relationship between infection and nutritional status in maintenance dialysis patients, and review interventions for improving clinical outcomes in this population. The relationship between inflammation and nutritional status will be the subject of a future column.

Components of the immune system

The immune system protects the body against invading microorganisms and consists of nonspecific mechanisms and a specific immune response.

Nonspecific mechanisms comprise nonadaptive immunity and include the physical barriers, mucosal secretions and enzymes provided by the skin, respiratory tract and gastrointestinal tract respectively (10). In addition, phagocytic cells including polymorphonuclear granulocytes ingest and destroy microorganisms. Neutrophils are granulocytes with potent bactericidal enzymes, while chemical granules in natural killer cells destroy virus-infected cells.

The specific immune response supplements nonspecific mechanisms and provides the ability to destroy microorganisms based on recognition of antigens on their cell membranes (10). Cell-mediated immunity involves specific cells of the immune system. T lymphocytes (T cells) detect and destroy foreign cells, and activate phagocytic cells. Macrophages, which develop from monocytes, recognize and bind antigens before presenting them to T cells. Humoral immunity refers to the actions of antibodies, or immunoglobulins (Ig), produced by ß-lymphocytes (ß cells) in attacking antigens.

Other key components of the immune system include complement, cytokines and eicosanoids. The complement system consists of proteins that defend the body against infectious agents by functioning as enzymes or binding proteins. Complement (e.g. C3, C4) promotes attachment of antibodies and phagocytes to antigens, and damages cell membranes of invading microorganisms. Cytokines are chemical messengers controlling multiplication of immune cells and stopping the immune response when it is no longer needed. Cytokines include the interleukins, which enhance the immune response, and tumor necrosis factor, which attracts phagocytic cells and promotes destruction of anti- gens. Eicosanoids, derived from fatty acids, include prostaglandins, leukotrienes, prostacyclins and thromboxanes. Collectively, eicosanoids control migration of phagocytic cells, regulate blood clot formation and direct proliferation of lymphocytes.

Infection and nutritional status in maintenance dialysis patients

Studies in animals and humans have demonstrated that nutritional deficiencies impair synthesis of molecules needed for the immune response, and increase infection and mortality rates.

Malnutrition has a significant impact on maturation of T cells, leading to a reduction in functional T cells and decreased ability to destroy foreign cells by phagocytosis (11). Specific nutritional deficiencies also have detrimental effects on immunocompetence. Inability to synthesize complement in protein malnutrition further impairs phagocytosis (11). Iron and zinc are prerequisites for nucleic acid synthesis and cell replication, and a deficiency of these minerals prevents an effective immune response to infection (11,12). Vitamin D deficiency is associated with increased susceptibility to infection (13). Immune system cells have vitamin D receptors, and vitamin D may enhance antibody-mediated immunity.

In patients with impaired renal function, cell-mediated immunodeficiency occurs in the early stages of CKD and worsens as renal failure progresses (14,15). The number of T cells is significantly reduced in patients undergoing maintenance HD for more than one year (16). This decline in T cells is accompanied by decreased

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phagocytic activity, an important predictor of infection-related hospitalizations (17).

Patients undergoing maintenance HD and PD also show significantly higher production of interleukins and tumor necrosis factor compared with healthy controls (18,19). When serum concentrations of these cytokines were measured in 331 maintenance HD patients, higher levels were associated with greater hospitalization rates, higher mortality and diminished appetite (20).

The relationship between nutritional status and immunocompetence has been evaluated in both the HD and PD patient populations. In a prospective, non-intervention study of protein-energy malnutrition (PEM) in 37 patients undergoing maintenance HD, a PEM score was derived at baseline and every 4 months based on serum albumin, body mass index (BMI), fat mass, fat-free mass and bone-free arm muscle area (21). Infection-related hospitalizations during a 26-month period showed significant correlation with both baseline and mean PEM scores. This suggests that PEM in maintenance HD patients is an important contributor to infection-related morbidity, possibly via its effects on the immune system.

Patients undergoing continuous ambulatory peritoneal dialysis (CAPD) were categorized according to the length of time they had been on dialysis and were assessed for nutritional status and immunocompetence (22). While body weight, BMI, fat stores and muscle mass were greater in patients who had been undergoing CAPD for a longer time period, protein intake was higher in patients beginning dialysis. Percentage of ß cells and immunoglobulins decreased with time on dialysis. These changes in immune cell numbers and immunoglobulins may be responsible for immunological disturbances and infectious processes in patients undergoing CAPD.

Interventions for improving clinical outcomes

As renal disease advances, immunocompetence declines and risk of infection is further increased by sub-optimal nutritional status in patients undergoing maintenance dialysis therapy (12,21,22). Improving nutritional status in maintenance dialysis patients decreases the risk of sepsis and vascular access infections (4,9).

The renal dietetics professional plays a key role in reducing infection risk in this population by monitoring nutritional status, providing nutrition education and encouraging adequate intake to meet nutritional needs.

Evidence suggests that fructo-oligosaccharides (FOS) occurring naturally in wheat, onions, bananas, honey, garlic and leeks, and incorporated into some medical nutritional formulas as NutraFlora®, may stimulate the immune system and decrease infection rates (23-25). FOS ingestion promotes growth of the bifidobacterium population in the large intestine (24). Acetic and lactic acids, along with other anti-microbial compounds produced by bifidobacteria, inhibit growth of Clostridium difficile and other pathogens (24-26).

Growth of the bifidobacterium population after FOS ingestion also results in immunoglobulin A secretion by Peyer's patch cells in the intestinal mucosa (27). These antibodies form the first line of immune defense by inhibiting attachment of microbes to the intestinal mucosa and destroying viruses intracellularly (28,29).

Recombinant human growth hormone (rhGH), which has been proposed as therapy for malnutrition due to its anabolic effects, has also been investigated for its impact on immune function. Administration of rhGH to maintenance HD patients results in significant increase in protein stores and improved muscle function (30,31). In a placebo-controlled, double blind study, phagocytic activity of polymorphonuclear granulocytes increased significantly in malnourished HD patients after 3 months of rhGH therapy and remained stable after 12 months of therapy (32,33). Thus, rhGH may provide a viable option in treating malnutrition and decreasing infection risk in this population.

It is likely, however, that medical nutrition therapy and anabolic growth factors will need to be combined with other therapeutic strategies to improve clinical outcomes. Patients with CKD frequently show high serum concentrations of cytokines, and appetite often improves when cytokine levels decline (8, 18-20). Cytokines may attach to receptors in the brain and stimulate release of eicosanoids, which also mediate anorexia (34). Targeting elevated cytokine and eicosanoid levels might therefore improve appetite and nutritional status.

Activity of the cytokine tumor necrosis factor has been blocked in persons with rheumatoid arthritis using monoclonal antibody therapy, and the possibility of using other substances to block cytokine and eicosanoid synthesis is under investigation (34,35). Another approach to cytokine removal is adsorption of these molecules onto a synthetic membrane during continuous venovenous hemofiltration (CVVH) (36).

Treatment of the anemia and secondary hyperparathyroidism often present in CKD also impacts the immune response and nutritional status. Intravenous iron therapy and iron overload have been linked to increased infection risk in HD patients (5). Findings from a recent study suggest that iron supplementation in patients receiving maintenance HD changes the balance of tumor necrosis factor and interleukins, to the detriment of the immune response to invading pathogens (37). This suggests that research is needed to determine the optimal iron dose for correcting anemia, while minimizing infection risk in these patients.

Parathyroid hormone (PTH) also has an adverse effect on the immune response, and treatment of secondary hyperparathyroidism with active vitamin D analogs may decrease the incidence of immunological disorders in patients with CKD (38). Treatment of HD patients with 1-alpha, 25-dihydroxyvitamin D3 has been shown to regulate monocytes and neutrophils, which play important roles in antigen binding and phagocytosis respectively (39). Maintenance dialysis patients with severe secondary hyperparathyroidism showed improvements in both nutritional status and humoral immunity 12 months after parathyroidectomy (40).

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Summary

A decrease in immunocompetence and increased infection risk accompany CKD. While infection affects nutritional status by contributing to anorexia, compromised nutritional status also increases infection risk. In order to break this cycle, renal dietetic professionals must provide aggressive medical nutrition therapy to meet their patients' macronutrient and micronutrient needs. Incorporating FOS into the diet may also enhance immunocompetence. Other potential therapies for improving the immune response and nutritional status in patients with CKD include rhGH and mechanisms for blocking the actions of cytokines and eicosanoids, which mediate anorexia. Proper attention to iron status and PTH levels may also impact the immune response and nutritional status.

References

1. Guarnieri G, Faccini L, Lipartiti T, Ranieri F, Spangaro F, Giuntini D, Toigo G, Dardi F, Berquier-Vidali F, Raimondi A. Simple methods for nutritional assessment in hemodialyzed patients. *Am J Clin Nutr.* 1980;33:1598-1607.
2. Mattern WD, Hak LJ, Lamanna RW, Teasley KM, Laffell MS. Malnutrition, altered immune function, and the risk of infection in maintenance hemodialysis patients. *Am J Kidney Dis*. 1982;1:206-218.
3. Bloembergen WE, Port FK. Epidemiological perspective on infections in chronic dialysis patients. *Adv Ren Replace Ther.* 1996;3:201-207.
4. Powe NR, Jaar B, Furth SL, Hermann J, Briggs W. Septicemia in dialysis patients: Incidence, risk factors, and prognosis. *Kidney Int.* 1999;55:1081-1090.
5. Teehan GS, Bahdouch D, Ruthazer R, Balakrishnan VS, Snydman DR, Jaber BL. Iron storage indices: Novel predictors of bacteremia in hemodialysis patients initiating intravenous iron therapy. *Clin Infect Dis*. 2004;38:1090-1094.
6. Maraj S, Jacobs LE, Maraj R, Kotler MN. Bacteremia and infective endocarditis in patients on hemodialysis. *Am J Med Sci.* 2004;327:242-249.
7. Maraj S, Jacobs LE, Kung SC, Raja R, Krishnasamy P, Maraj R, Braitman LE, Kotler MN. Epidemiology and outcome of infective endocarditis in hemodialysis patients. *Am J Med Sci.* 2002;324:254-260.
8. Aguilera A, Codoceo R, Bajo MA, Iglesias P, Diez JJ, Barril G, Cigarran S, Alvarez V, Celadilla O, Fernandez-Perpen A, Montero A, Selgas R. Eating behavior disorders in uremia: A question of balance in appetite regulation. *Semin Dial.* 2004;17:44-52.
9. Adeniyi OA, Tzamaloukas AH. Relation between access-related infection and preinfection serum albumin concentration in patients on chronic hemodialysis. *Hemodialysis International.* 2003;7:304-310.
10. Kline DA. *Nutrition and Immunity. Part 1: Immune Components and Nutrients*. 5th ed. Eureka, CA: Nutrition Dimension, Inc.;2002.
11. Keusch GT. The history of nutrition: Malnutrition, infection and immunity. *J Nutr.* 2003;133:336S-340S.
12. Fraker PJ, King LE, Laakko T, Vollmer TL. The dynamic link between the integrity of the immune system and zinc status. *J. Nutr.* 2000; 130 (suppl 5S) 1399S-1406S.
13. Hayes CE, Nashold FE, Spach KM, Pedersen LB. The immunological functions of the vitamin D endocrine system. *Cell Mol Biol.* 2003;49:277-300.
14. Giacchino F, Alloatti S, Quarello F, Bosticardo GM, Giraudo G, Piccoli G. The immunological state in chronic renal insufficiency. *Int J Artif Organs*. 1982;5:237-242.
15. Vanholder R, Ringoir S. Infectious morbidity and defects of phagocytic function in end-stage renal disease: A review. *J Am Soc Nephrol.* 1993;3:1541-1554.
16. Raska K Jr, Raskova J, Shea SM, Frankel RM, Wood RH, Lifter J, Ghobrial I, Eisinger RP, Homer L. T cell subsets and cellular immunity in end-stage renal disease. *Am J Med.* 1983;75:734-740.
17. Vanholder R, Ringoir S, Dhondt A, Hakim R. Phagocytosis in uremic and hemodialysis patients: A prospective cross sectional study. *Kidney Int.* 1991;39:320-327.
18. Malaponte G, Bevelacqua V, Fatuzzo P, Rapisarda F, Emmanuele G, Travali S, Mazzarino MC. IL-1 beta, TNF-alpha and IL-6 release from monocytes in haemodialysis patients in relation to dialytic age. *Nephrol Dial Transplant.* 2002;17:1964-1970.
19. Klinger J, Enriquez J, Arturo JA, Delgado M, Avila G, Ceballos O. Cytokines and peritonitis in continuous ambulatory peritoneal dialysis: Immunodeviation and immunodeficiency. *Adv Perit Dial.* 2002;18:170-176.
20. Kalantar-Zadeh K, Block G, McAllister CJ, Humphreys MH, Kopple JD. Appetite and inflammation, nutrition, anemia and clinical outcome in hemodialysis patients. *Am J Clin Nutr.* 2004;80:299-307.
21. Herselman M, Moosa MR, Kotze TJ, Kritzinger M, Wuister S, Mostert D. Protein-energy malnutrition as a risk factor for increased morbidity in long-term hemodialysis patients. *J Ren Nutr.* 2000;10:7-15.
22. Palop L, Martinez JA. Cross-sectional assessment of nutritional and immune status in renal patients undergoing continuous ambulatory peritoneal dialysis. *Am J Clin Nutr.* 1997;66:498S-503S.
23. Chow J. Probiotics and prebiotics: A brief overview. *J Ren Nutr.* 2002;12:76-86.
24. Ross Products Division Abbot Laboratories Inc. *Fructooligosaccharides*. April 2002.
25. GTC Nutrition Company. *NutraFlora® and its role in medical nutrition therapy*. 1999.
26. Gibson GR, Wang X. Regulatory effects of bifidobacteria on the growth of other colonic bacteria. *J Appl Bacteriol.* 1994;77:412-420.
27. Hosono A, Ozawa A, Kato R, Ohnishi Y, Nakanishi Y, Kimura T, Nakamura R. Dietary fructooligosaccharides induce immunoregulation of intestinal IgA secretion by murine Peyer's patch cells. *Biosci Biotechnol Biochem.* 2003;67:758-764.
28. Lamm ME. Current concepts in mucosal immunity. IV. How epithelial transport of IgA antibodies relates to host defense. *Am J Physiol.* 1998;274: G614-G617.
29. Lamm ME. Interaction of antigens and antibodies at mucosal surfaces. *Annu Rev Microbiol.* 1997;51:311-340.
30. Schulman G, Wingard RL, Hutchison RL, Lawrence P, Hakim RM. The effects of recombinant human growth hormone and intradialytic parenteral nutrition

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in malnourished hemodialysis patients. *Am J Kidney Dis*. 1993;21:527-534.

31. Johannsson G, Bengtsson BA, Ahlmen J. Double-blind, placebo-controlled study of growth hormone treatment in elderly patients undergoing chronic hemodialysis: Anabolic effect and functional improvement. *Am J Kidney Dis*. 1999;33:709-717.
32. Kotzmann H, Yilmaz N, Lercher P, Riedl M, Schmidt A, Schuster E, Kreuzer S, Geyer G, Frisch H, Horl WH, Mayer G, Luger A. Differential effects of growth hormone therapy in malnourished hemodialysis patients. *Kidney Int*. 2001;60:1578-1585.
33. Kotzmann H, Schmidt A, Lercher P, Schuster E, Geyer G, Frisch H, Horl WH, Mayer G, Luger A. One-year growth hormone therapy improves granulocyte function without major effects on nutritional and anthropometric parameters in malnourished hemodialysis patients. *Nephron Clin Pract*. 2003;93:C75-82.
34. Langhans W. Anorexia of infection: Current prospects. *Nutrition*. 2000;16:996-1005.
35. Elliott MJ, Maini RN, Feldmann M, Kalden JR, Antoni C, Smolen JS, Leeb B, Breedveld FC, Macfarlane JD, Bijl H. Randomised double-blind comparison of chimeric monoclonal antibody to tumor necrosis factor alpha (cA2) versus placebo in rheumatoid arthritis. *Lancet*. 1994;344:1105-1110.
36. De Vriese AS, Colardyn FA, Philippe JJ, Vanholder RC, De Sutter JH, Lameire NH. Cytokine removal during continuous hemofiltration in septic patients. *J Am Soc Nephrol*. 1999;10:846-853.
37. Weiss G, Meusburger E, Radacher G, Garimorth K, Neyer U, Mayer G. Effect of iron treatment on circulating cytokine levels in ESRD patients receiving recombinant human erythropoietin. *Kidney Int*. 2003;64:572-578.
38. Shoji T, Shinohara K, Kimoto E, Emoto M, Tahara H, Koyama H, Inaba M, Fukumoto S, Ishimura E, Miki T, Tabata T, Nishizawa Y. Lower risk for cardiovascular mortality in oral 1 alpha-hydroxy vitamin D3 users in a hemodialysis population. *Nephrol Dial Transplant*. 2004;19:179-184.
39. Tokuda N, Kano M, Meiri H, Nomoto K, Naito S. Calcitriol therapy modulates the cellular immune responses in hemodialysis patients. *Am J Nephrol*. 2000;20:129-137.
40. Yasunaga C, Nakamoto M, Matsuo K, Nishihara G, Yoshida T, Goya T. Effects of parathyroidectomy on the immune system and nutritional condition in chronic dialysis patients with secondary hyperparathyroidism. *Am J Surg*. 1999;178:332-336.

RPG Election Results:

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Impact of Infection and the Immune Response on Nutritional Status in Patients with Chronic Kidney Disease Undergoing Maintenance Dialysis Therapy

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Objective: Participant will learn the roles that infection and the immune response may have on the nutritional status of patients with CKD undergoing dialysis.

This activity is approved for 1.0 CPEU, Level 3, by the Commission on Dietetic Registration (CDR) for registered dietitians and dietetic technicians, registered who are members of the Renal Practice Group. Valid through May 31, 2006. After reading the continuing professional education article, please answer the following questions by indicating your responses on the self-assessment questionnaire form (see insert). Please be sure to submit your registration number and write legibly, or you may not receive credit. Upon mailing the questionnaire to the assistant editor, you may fill out the certificate of completion on page 13, retain it in your portfolio, and record the activity on your Step Activity Log. Members will not receive mailed certificates of completion. Answers to the continuing professional education questions can be found on page 13.

Multiple Choice

1. Examples of specific immune response include:
   A. Gastrointestinal tract enzymes
   B. Mucosal secretions
   C. Physical barriers
   D. None of the above

2. Which of the following treatments pose a link to increased infection risk by changing the balance of tumor necrosis factor and interleukins to the detriment of the immune response?
   A. EPO therapy
   B. Intravenous iron therapy
   C. Treatment of secondary hyperparathyroidism
   D. Parathyroidectomy

3. _____ are chemical messengers controlling multiplication of immune cells and stopping the immune response when no longer needed.
   A. Cytokines
   B. Neutrophils
   C. Phagocytic cells
   D. T cells

4. The roles of the complement system (C3, C4) include all except one below
   A. Attachment of antibodies to antigens
   B. Attachment of phagocytes to antigens
   C. Destroying cell walls of bacteria
   D. Damaging cell membranes of invading microorganisms

5. Examples of nutrient deficiencies which impair the immune system include
   A. All of below
   B. Lack of vitamin D
   C. Lack of iron
   D. Lack of zinc

6. Fructooligosaccharides (FOS) may stimulate the immune system and decrease infection rates by all except one of the following
   A. Promoting growth of clostridium difficile through NutraFlora®
   B. Promoting growth of the bifidobacterium population in the large intestine
   C. Promoting antibodies by inhibiting attachment of microbes to the intestinal mucosa
   D. Destroying viruses intracellularly

7. Lowering levels of cytokines could
   A. Improve appetite
   B. Be accomplished by using monoclonal antibody therapy
   C. Be accomplished by CVVH
   D. All of the above

8. Recombinant human growth hormone (rhGH) may be a viable option to improving malnutrition and decreasing infection risk through multiple pathways?
   A. True
   B. False

9. USRDS indicates overall hemodialysis patients have a higher infection death risk than peritoneal dialysis due to catheter sepsis.
   A. True
   B. False

10. Cell-mediated immunodeficiency occurs in the late stages of CKD and worsens as renal failure progresses.
    A. True
    B. False