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Nutritional Management of Diabetic Renal Transplant Recipients

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This chapter provides the necessary background information required for a health care professional to give dietary advice to a diabetic renal transplant recipient. The chapter covers the main causes of morbidity and mortality in diabetic renal transplant patients and examines whether dietary intervention can improve graft survival and clinical outcome.

INTRODUCTION

RENAL TRANSPLANTATION AND DIABETES

End stage renal failure (ESRF) from diabetes is increasing and the number of diabetic patients receiving a renal transplant is growing. Diabetes is also a common metabolic complication following a successful renal transplant, due partly to the steroids used to prevent graft rejection and to the associated weight gain they cause. In one study involving 114 patients with normal glucose tolerance, a week before transplantation, only 36 (32%) retained normal glucose tolerance 9 to 12 months post-transplant with 27 (24%) patients becoming frankly diabetic. Both β-cell dysfunction and insulin resistance contribute to the development of diabetes post-transplant (1,2).

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MORBIDITY AND MORTALITY

Transplantation provides the best renal replacement option for diabetic patients with ESRF, improving the quality of life (3,4), and resulting in less neuropathy and anorexia. Unfortunately, renal transplantation does not improve pre-existing metabolic conditions such as dyslipidaemia or bone disease. These continue to progress and contribute to the long-term morbidity and mortality. The medications used to prevent graft rejection also contribute to metabolic risk factors, including weight gain and metabolic bone disease.

Five-year survival rates are higher following a renal transplant than with regular dialysis, especially for people with diabetes. Despite this, five-year survival rates for diabetic patients are still appreciably lower (66–75%) than for non-diabetic patients (90–95%) (5,6). Mortality rates are lower when diabetic patients receive a combined kidney–pancreas transplant than an isolated kidney (6,7). To what extent this is due to improved glycaemic control is uncertain, as patient selection criteria for a dual kidney–pancreatic transplant inevitably select patients with low co-morbidity scores. Diabetic microvascular disease, retinopathy and neuropathy improve initially following renal transplantation. The neuropathy improvement is however more sustained in patients receiving a combined kidney–pancreas transplant (8,9).

Ischaemic heart disease is present in 40% of diabetic patients prior to transplant (3,4), and when present carries a threefold risk of a further coronary event over the next four years (5). The higher mortality rate of diabetic compared to non-diabetic renal transplant recipients is mainly related to this high incidence of pre-existing coronary heart disease. In a four-year follow-up study of 101 transplant patients with Type 1 diabetes, the absolute mortality rate was 30%, with 57% of these deaths attributed to arterial disease (5). Peripheral vascular disease also progresses after a renal transplant, and the risk of ulcers and poor wound healing is increased in these immunocompromised patients.

DIETARY INTERVENTION STUDIES

A 20-year literature search identifies few dietary intervention studies in renal transplant patients. The number of subjects included in these intervention and observational studies is small and many of these short studies fail to adequately differentiate the effects of diet and medication, see Table 16.1.

KIDNEY SURVIVAL

A transplanted kidney is susceptible to hyperglycaemia and hypertension (3,4). Hypercholesterolaemia and hypertriglyceridaemia also influence graft survival

Table 16.1 Dietary intervention and observational studies in renal transplant recipients

Author	Study protocol	Outcome
Patel (30)	Four months' diet and lifestyle advice given to 11 new transplant patients compared to 22 patients previously transplanted in the previous four years receiving no dietary advice	There was a significantly lower weight gain at four months and one year in the group given dietary advice than in the historical controls receiving no dietary advice (5.5 kg vs 11.8 kg)
Tonstad *et al.* (26)	26 patients post-transplant given a Step 1 American Heart Association diet for 12 weeks <30% total calories from fat <300 mg cholesterol/day <10% total calories from saturated fat	Weighed dietary records showed a decrease in total fat (30 to 27%) and a fall in saturated fat (12 to 8% of total calories). Body weight and lipids profile remained unchanged, apart from a small fall in triglyceride values in patients with a BMI < 26 kg/m^2
Hines (31)	$N = 43$. Step 1 American Heart Association diet prescribed for two to eight months	Total cholesterol decreased significantly by 0.54 mmol/l, LDL-cholesterol by 0.53 mmol/l. In all 20% of patients reached target levels of total cholesterol < 5.2 mmol/l and 35% of patients reached the LDL-cholesterol target of < 3.5 mmol/l. Total fat intake fell by 7.6% of total calories
Barbagallo *et al.* (32)	$N = 78$ normal and hyperlipidaemic subjects given a Step 1 American Heart Association diet for 12 weeks that was isocaloric with usual diet	Cholesterol reduced by 10% (6.02 to 5.41 mmol/l), triglyceride by 6.5% (1.81 to 1.7 mmol/l). Improvements in LDL-cholesterol occurred in patients with high starting LDL-cholesterol levels
Foldes *et al.* (24)	$N = 21$diabetic transplant patients, given a diet for eight weeks and followed for one year	No change in lipid profile with diet, but significant decrease in total cholesterol after 12 weeks when patients were also given fluvastatin
Lal *et al.* (33)	Step I and 2 American Heart Association diet given to non-DM transplant patients	No significant change in total cholesterol or triglyceride
La Rocca *et al.* (25)	Dietary advice and lipid management in Type 1 diabetic patients receiving a kidney or a kidney and pancreatic transplant	There was a decrease in total fat and cholesterol intake in both groups and a significant decrease in plasma cholesterol in the kidney-pancreas transplant group from 5.3–4.9 mmol/L
Moore *et al.* (21)	18 patients (four diabetic) given an American Heart Association Step 1 diet (also weight reducing and low sodium) with a serum cholesterol > 200 mg/dl	Weight loss 2 lb. Cholesterol decreased from 262 to 241 mg/dl after eight weeks

(10–12). The benefits of good glycaemic control on graft survival may however require three or more years to become apparent. The rationale for optimising glycaemic control is based on the knowledge that prior to transplant poor glycaemic control influences glomerular filtration loss, and that long-term graft survival following a combined kidney and pancreas transplant (K-P) is better than for an isolated kidney (13,14). Improved lipoprotein concentrations are also observed after K-P transplantation and this again is attributable to better glycaemic control (15).

Low-protein diets in the diabetic patients with CRF have been shown to have a beneficial effect on disease progression and proteinuria. A number of studies in (mostly non-diabetic) transplant patients have shown that reducing protein intake may improve graft survival and slow the progression of renal disease in chronic rejection (16–18). Hyperlipidaemia prior to, and following, transplant is also associated with an increased risk of graft rejection (12).

There is a suggestion that fish oils can protect the kidney in cyclosporine-treated renal transplant recipients. However the role of omega-3 unsaturated fatty acid supplementation remains controversial. In one randomised prospective controlled trial early dietary supplementation post-transplant with daily 6 g fish oil for one month favourably influenced renal function in the recovery phase following a rejection episode in patients treated with cyclosporine (19,20). In another study although patients taking 6 g/day of fish oils did not show any improvement in rejection rates at one year they did have a non-significant improvement in their renal function (20). The role of dietary intervention with antioxidants and diets to decrease PAI-1 synthesis in renal transplant recipients requires further evaluation.

CARDIOVASCULAR DISEASE

Both renal disease and diabetes are associated with accelerated CVD. The sedentary lifestyle adopted by many renal patients exacerbates weight gain and many of the recognised metabolic risk factors attached to this. Dietary advice needs to address the usual modifiable CVD risk factors in this group. It could be argued that a diabetic with a functioning renal transplant should receive the same advice as other diabetics without renal failure. However, the response to diet therapy may not be similar due to the anti-rejection medications prescribed (21).

Obesity prior to a renal transplant is associated with higher five-year mortality rates. In one study of 127 obese ($BMI > 31\,kg/m^2$) non-diabetic renal transplant recipients the five-year survival rate was 67%. This was significantly lower than the 89% observed in the 127 non-obese ($BMI < 27\,kg/m^2$) non-diabetic renal transplant recipients (22). Most of this excess mortality can be attributed to cardiac disease. Even if weight loss cannot be achieved prior to transplantation, intensive dietary advice is required post-transplant to limit the

usual weight gains that occur. In one study of non-diabetic patients the percentage of patients who had a BMI $> 25\,kg/m^2$ increased from 22% to 36% post-transplantation (23).

There are a few dietary intervention studies that deal specifically with diabetic patients post-transplantation (15,24,25). However these studies only involve small numbers of patients followed for a relatively short period of time, and none adequately separate the effects of diet from the effects of medication. In non-diabetic transplant patients the effectiveness of the Step 1 American Heart Association diet to reduce weight gains and improve lipid profiles has been very variable. Even when significant weight loss is achieved, by six months, lipid profiles do not always improve. Hyperlipidaemia appears to be related more to renal impairment than dietary fat modification, especially if weight reduction does not occur (26). Population studies have shown that a reduced-fat diet is required for at least two years to achieve any reduction in cardiovascular events, and this possibly explains the disappointing results of shorter-term studies in post-transplantation patients (see Table 16.1).

Hyperhomocysteinaemia (tHcy) is another independent risk factor for coronary heart disease (27). Both Type 1 and Type 2 diabetic patients with renal failure have approximately fourfold higher tHcy levels than controls prior to transplantation. These levels can fall by a third after a successful renal transplant and further falls have been reported with folic acid, B6 and B12 supplements (28). The routine place of these dietary supplements in diabetic renal transplant patients awaits further studies.

TREATMENT STRATEGIES

For diabetic renal transplant recipients with pre-existing heart disease the lipid-lowering drugs, belonging to the class of HMG-CoA reductase inhibitors, and universally known as the 'statins', are thought to be more effective at reducing cholesterol levels than advocating a low-cholesterol diet. However there are no studies in the diabetic renal transplant population that allow us to judge whether these drugs are as effective at reducing cardiovascular disease as in the general diabetic population. Controlled studies on transplant patients examining 'healthy' eating, lifestyle changes, glycaemic control and the use of fish oils, vitamins and other 'functional foods' are required to determine their benefit in graft survival and long-term cardiovascular health.

BONE DISEASE

Metabolic bone disease continues to influence morbidity and mortality after a successful transplant. Despite normalisation of phosphate excretion and

improved activation of vitamin D, parathyroid hormone levels can remain elevated. Bone resorption continues due to the adverse effects of corticosteroids on osteoblast function and calcium absorption from the gut. Type 1 diabetic transplant recipients have been reported to have a higher fracture rate than non-diabetic recipients (40% vs 11%) (29). This increased fracture rate is similar in the male and female diabetic subjects, and contrasts with results from the non-diabetic transplant recipients in whom the female fracture rate is approximately twice that of men. Increased intake of dietary calcium and the use of calcitriol and alendronate can help to neutralise the adverse effect of corticosteroids.

CONCLUSION

Renal transplantation offers diabetic patients an improved quality of life and longevity. Metabolic risk factors can be exacerbated by the immunosuppresion needed to minimise graft rejection. Dietary advice to limit post-transplant weight gain should be given along with advice aimed at meeting protein requirements, improving glycaemic control and hyperlipidaemia and reducing the risk of metabolic bone disease. The impact of this type of dietary advice on overall morbidity and mortality remains to be fully evaluated.

REFERENCES

1. Jindal RM, Hjelmesaeth J. Impact and management of posttransplant diabetes mellitus. *Transplantation* 2000; 70 (Suppl 11): S58–S63.
2. Hjelmesæth J, Midtvedt K, Jenssen T, Hartmann A. Insulin resistance after renal transplantation: impact of immunosuppressive and antihypertensive therapy. *Diabetes Care* 2001; 24: 2121–2126.
3. Ritz E, Stefanski A. Diabetic nephropathy in type II diabetes. *Am J Kidney Dis* 1996; 27: 167–194.
4. Ritz E, Keller C, Bergis K, Strojek K. Pathogenesis and course of renal disease in IDDM/NIDDM. *Am J Hypertens* 1997; 10 (9/2): 202S–207S.
5. Lemmers MJ, Barry JM. Major role for arterial disease in morbidity and mortality after kidney transplantation in diabetic recipients. *Diabetes Care* 1991; 14: 295–301.
6. Carlstrom J, Norden G, Mjornstedt L, Nyberg G. Increasing prevalence of cardiovascular disease in kidney transplant patients with Type 1 diabetes. *Transpl Int* 1999; 12: 176–181.
7. Biesenbach G, Margreiter R, Konigsrainer A, Bosmuller C, Janko O, Brucke P, Gross C, Zazgornik J. Comparison of progression of macrovascular diseases after kidney or pancreas and kidney transplantation in diabetic patients with end-stage renal disease. *Diabetologia* 2000; 43: 231–234.
8. Adang EM, Engel GL, van Hooff JP, Kootstra G. Comparison before and after transplantation of pancreas–kidney and pancreas–kidney with loss of pancreas – a prospective controlled quality of life study. *Transplantation* 1996; 62: 754–758.

9. Ekstrand A, Groop L, Pettersson E, Gronhagen-Riska C, Laatikainen L, Matikainen E, Seppalainen AM, Laasonen E, Summanen P, Ollus A *et al*. Metabolic control and progression of complications in insulin-dependent diabetic patients after kidney transplantation. *J Intern Med* 1992; 232: 253–261.
10. Dimeny E, Wahlberg J, Lithell H, Fellstrom B. Hyperlipidaemia in renal transplantation – risk factor for long-term graft outcome. *Eur J Clin Invest* 1995; 25: 574–583.
11. Dimeny E, Fellstrom B. Metabolic abnormalities in renal transplant recipients. Risk factors and predictors of chronic graft dysfunction? *Nephrol Dial Transplant* 1997; 12: 21–24.
12. Hamar P, Muller V, Kohnle M, Witzke O, Albrecht KH, Philipp T, Heemann U. Metabolic factors have a major impact on kidney allograft survival. *Transplantation* 1997; 64: 1135–1139.
13. Solders G, Tyden G, Persson A, Groth CG. Improvement of nerve conduction in diabetic neuropathy. A follow-up study 4 yr after combined pancreatic and renal transplantation. *Diabetes* 1992; 41: 946–951.
14. Manske CL, Wang Y, Thomas W. Mortality of cadaveric kidney transplantation versus combined kidney–pancreas transplantation in diabetic patients. *Lancet* 1995; 346: 1658–1662.
15. Georgi BA, Bowers VD, Smith JL, Wright FH, Corry RJ. Comparison of fasting serum cholesterol levels between diabetic recipients who undergo renal–pancreas transplants and renal transplantation only. *Transplant Proc* 1989; 21 (1/3): 2839–2840.
16. Bernardi A, Biasia F, Piva M, Poluzzi P, Senesi G, Scaramuzzo P, Garizzo O, Stoppa F, Cavallaro B, Bassini S, Bucciante G. Dietary protein intake and nutritional status in patients with renal transplant. *Clin Nephrol* 2000; 53: 3–5.
17. Biesenbach G, Zazgornik J, Janko O, Hubmann R, Syre G. Effect of mild dietary protein restriction on urinary protein excretion in patients with renal transplant fibrosis. *Wien Med Wochenschr* 1996; 146: 75–78.
18. Salahudeen AK, Hostetter TH, Raatz SK, Rosenberg ME. Effects of dietary protein in patients with chronic renal transplant rejection. *Kidney Int* 1992; 41: 183–190.
19. Homan van der Heide JJ, Bilo HJ, Donker AJ, Wilmink JM, Sluiter WJ, Tegzess AM. The effects of dietary supplementation with fish oil on renal function and the course of early postoperative rejection episodes in cyclosporine-treated renal transplant recipients. *Transplantation* 1992; 54: 257–263.
20. Kooijmans-Coutinho MF, Rischen-Vos J, Hermans J, Arndt JW, van der Woude FJ. Dietary fish oil in renal transplant recipients treated with cyclosporin-A: no beneficial effects shown. *J Am Soc Nephrol* 1996; 7: 513–518.
21 Moore RA, Callahan MF, Cody M, Adams PL, Litchford M, Buckner K, Galloway J. The effect of the American Heart Association step one diet on hyperlipidemia following renal transplantation. *Transplantation* 1990; 49: 60–62.
22. Modlin CS, Flechner SM, Goormastic M, Goldfarb DA, Papajcik D, Mastroianni B, Novick AC. Should obese patients lose weight before receiving a kidney transplant? *Transplantation* 1997; 64: 599–604.
23. Locsey L, Asztalos L, Kincses Z, Berczi C, Paragh G. The importance of obesity and hyperlipidaemia in patients with renal transplants. *Int Urol Nephrol* 1998; 30: 767–775.
24. Foldes K, Maklary E, Vargha P, Janssen J, Jaray J, Perner F, Gero L. Effect of diet and fluvastatin treatment on the serum lipid profile of kidney transplant, diabetic recipients: a 1-year follow up. *Transpl Int* 1998; 11 (Suppl 1): S65–S68.

25. La Rocca E, Ruotolo G, Parlavecchia M, Librenti MC, Secchi A, Caldara R, Bonfatti D, Bernardi M, Di Carlo V, Pozza G. Dietary advice and lipid metabolism in insulin-dependent diabetes mellitus kidney- and pancreas-transplanted patients. *Transplant Proc* 1992; 24: 848–849.
26. Tonstad S, Holdaas H, Gorbitz C, Ose L. Is dietary intervention effective in post-transplant hyperlipidaemia?. *Nephrol Dial Transplant* 1995; 10: 82–85.
27. Ducloux D, Motte G, Massy ZA. Hyperhomocysteinemia as a risk factor after renal transplantation. *Ann Transplant* 2001; 6: 40–42.
28. Socha MW, Polakowska MJ, Socha-Urbanek K, Fiedor P. Hyperhomocysteinemia as a risk factor for cardiovascular diseases. The association of hyperhomocysteinemia with diabetes mellitus and renal transplant recipients. *Ann Transplant* 1999; 4: 11–19.
29. Nisbeth U, Lindh E, Ljunghall S, Backman U, Fellstrom B. Increased fracture rate in diabetes mellitus and females after renal transplantation. *Transplantation* 1999; 67: 1218–1222.
30. Patel MG. The effect of dietary intervention on weight gains after renal transplantation. *J Ren Nutr* 1998; 8: 137–141.
31. Hines L. Can low-fat/cholesterol nutrition counseling improve food intake habits and hyperlipidemia of renal transplant patients? *J Ren Nutr* 2000; 10: 30–35.
32. Barbagallo CM, Cefalu AB, Gallo S, Rizzo M, Noto D, Cavera G, Rao Camemi A, Marino G, Caldarella R, Notarbartolo A, Averna MR. Effects of Mediterranean diet on lipid levels and cardiovascular risk in renal transplant recipients. *Nephron* 1999; 82: 199–204.
33. Lal SM, Trivedi HS, Van Stone JC, Ross G Jr. Effects of dietary therapy on post renal transplant hyperlipidemia. A prospective study. *Int J Artif Organs* 1994; 17: 461–465.