

Nutritional management of dyslipidaemia in adult kidney transplant recipients

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GUIDELINES

No recommendations possible based on Level I or II evidence.

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on Level III and IV evidence)

Once graft is functioning:

- A diet rich in wholegrain, low glycaemic index and high fibre carbohydrates as well as rich sources of vitamin E and monounsaturated fat should be recommended to adult kidney transplant recipients with elevated serum total cholesterol, LDL-cholesterol and triglycerides. (Level III–IV)
- Weight reduction in overweight or obese kidney transplant recipients should be encouraged and supported. (Level IV) (Refer to CARI Guideline: Nutritional management of overweight and obesity in adult kidney transplant patients)
- Kidney transplant recipients with dyslipidaemia should be advised to eat a diet which reflects the evidence described above while being in line with lipid management guidelines for the general population as follows:

1 Carbohydrate

Carbohydrate should be consumed predominantly in the form of wholegrains and foods with a low energy density and/or low glycaemic index, aiming for a daily fibre intake of 25 g for females and 30 g for males. The inclusion of the soluble fibre beta-glucan should be encouraged as it has been shown to lower LDL-cholesterol in non-transplant populations.^{1–4}

2 Fat

Total fat should contribute 30–35% of total energy intake. Saturated and *trans* fatty acids together should contribute no more than 8% of total energy intake. n-6 polyunsaturated fat should contribute 8–10% of total energy. Monounsaturated fat may contribute up to 20% of total energy intake. n-3 polyunsaturated fat should be included in the diet as both plant and marine sources.^{1,2,5}

3 Plant sterols and stanols

Include plant foods which are naturally rich in phytosterols as well as 2–3 g phytosterol-enriched food products (such as margarine, breakfast cereal, low fat yoghurt or milk enriched with phytosterols. Australian regulations allow a minimum of 0.8 g and a maximum

of 1.0 g phytosterols per serve of food, thus two or three serves of phytosterol-fortified foods should be recommended.^{6,7}

- Alcohol should be limited to no more than two standard drinks on any day for both men and women. This advice is based on NHMRC guidelines for lifetime health risks associated with daily alcohol consumption by 'healthy' men and women.⁸ The potential direct effect of alcohol consumption on serum lipids, as well as the energy yield of alcohol (29 kilojoules per gram) and the contribution it may make to excessive energy intake and weight gain, should also be considered.⁹

BACKGROUND

Dyslipidaemia is common after renal transplantation, estimated to be present in around 60% of kidney transplant recipients. The definition of dyslipidaemia which has been adopted by the National Kidney Foundation KDOQI,¹⁰ based on that of the Adult Treatment Panel III,¹¹ is the presence of one or more of the following: total serum cholesterol >200 mg/dL; LDL-cholesterol >130 mg/dL; triglycerides >150 mg/dL; HDL-cholesterol <40 mg/dL. The typical lipid profile of transplant recipients includes elevated total serum cholesterol and low-density lipoprotein cholesterol (LDL-C), with variable high-density lipoprotein cholesterol (HDL-C) and triglycerides.^{12–15} Studies have shown that lipoprotein abnormalities are a persistent problem even 10 years post-transplant.^{16,17}

The correlation between dyslipidaemia and cardiovascular disease (CVD) risk in non-transplant populations has been well established.¹¹ Several studies have reported a positive association between total cholesterol and atherosclerotic CVD in kidney transplant recipients, similar to that observed in the general population.¹⁸

Compared with the general population, transplant recipients may develop lipoprotein alterations that have a potentially more atherogenic profile. Indeed, statistics show that CVD mortality rates among organ transplant recipients are up to 10-fold those in the non-transplant population.^{19–23}

While dyslipidaemia and CVD are often present at the time of transplantation, immunosuppressive medications (such as calcineurin inhibitors, sirolimus and corticosteroids), lifestyle factors and post-transplant renal function are also implicated in abnormal serum lipid levels and CVD risk post-transplantation.^{24–30}

Guidelines for the management of dyslipidaemias in the general population make recommendations on diet and other aspects of lifestyle including exercise, body weight, alcohol consumption and smoking.^{1,2,5,31–33}

The objective of this guideline is to ensure that appropriate dietary interventions are used to prevent and manage dyslipidaemia in adult kidney transplant recipients.

SEARCH STRATEGY

Relevant reviews and studies were obtained from the sources below and reference lists of nephrology textbooks, review articles and relevant trials were also used to locate studies. Searches were limited to studies on humans; adult kidney transplant recipients; single organ transplants and to studies published in English. Unpublished studies were not reviewed.

Databases searched: MeSH terms and text words for kidney transplantation were combined with MeSH terms and text words for both dyslipidaemia and dietary interventions. Dietary fish oil and fish oil supplements were not included in the search as this literature review has been undertaken previously. MEDLINE – 1966 to week 1, September 2006; EMBASE – 1980 to week 1, September 2006; the Cochrane Renal Group Specialised Register of Randomised Controlled Trials.

Date of searches: 22 September 2006.

WHAT IS THE EVIDENCE?

There are few published studies of satisfactory quality examining the safety and efficacy of specific dietary interventions in the management of dyslipidaemia in kidney transplant recipients.

Level I/II: There are no randomized controlled trials investigating the efficacy of nutritional interventions for treating dyslipidaemia in kidney transplant recipients.

Level III: There is one study of satisfactory quality providing level III-1 evidence that a modified Mediterranean-style diet (rich in high fibre, low glycaemic index carbohydrates; vegetables; vitamin E-rich foods; and sources of monounsaturated fatty acids) may lower serum total cholesterol and triglycerides in kidney transplant recipients.³⁴

Level IV: There is one study providing level IV evidence that a diet low in carbohydrate and high in polyunsaturated fat may be effective in normalizing HDL-cholesterol and may lead to weight loss in adult kidney transplant recipients.³⁵

There is one level IV (pre-test, post-test study) of satisfactory quality investigating the safety and efficacy of a modified version of the American Heart Association

(AHA) Step One diet. This diet, rich in high fibre carbohydrates, vegetables, vitamin E-rich foods and sources of monounsaturated fatty acids, appears to be effective in lowering serum total cholesterol and triglycerides in kidney transplant recipients.³⁶ A third study provides level IV evidence that weight loss appears to be associated with a fall in total cholesterol in kidney transplant recipients.³⁷

The recommendation that a diet rich in wholegrain, low glycaemic index and high fibre carbohydrates as well as rich sources of vitamin E and monounsaturated fat should be followed by adult kidney transplant recipients with elevated serum total cholesterol, LDL-cholesterol and triglycerides, is based on evidence from the following three studies:

1 Modified Mediterranean diet

Stachowska *et al.*³⁴ investigated the effect of a modified Mediterranean diet on serum lipid levels in a single-centre, randomized controlled study. Adult kidney transplant recipients with stable graft function were randomized to receive one of two diets for a 6-month period:

- **Treatment:** Modified Mediterranean diet ($n = 21$; 15 males, six females), containing carbohydrates with a low glycaemic index (amylose-poor, cellulose-rich), 30 mL cold-pressed olive oil with only rapeseed oil used in cooking, foods rich in alpha-tocopherol (including nuts, grains and linseeds), fresh vegetables with each meal and daily animal protein of 35–50 g for males and 23–46 g for females. Energy intake was attributed as follows: 47% carbohydrates, 38% fat, 15% protein.

- **Control:** Standard low fat diet, typical of the Central European dietary pattern ($n = 16$, 10 males, six females), which was isocaloric with treatment diet. Glycaemic index was markedly higher. Energy intake was attributed as follows: 57% carbohydrates, 26% fat, 17% protein.

Immunosuppressive and antihypertensive regimens were not changed and no antilipemic medications were administered before or during the study period. Dietary compliance of subjects in both groups was assessed every 4 weeks by means of 24 h food diaries and by monitoring oleic acid content of plasma triglycerides.

In the treatment group, total cholesterol dropped from 230 to 210 mg/dL, or 5.9–5.4 mmol/L ($P < 0.02$) and triglycerides dropped from 194 to 152 mg/dL, or 2.5–1.7 mmol/L ($P < 0.0007$). Neither total cholesterol nor triglycerides dropped in the control group. There was no significant difference between the groups with respect to weight, body mass index and body fat levels at the start or the end of the study period.

The key limitations of this study are:

- the small sample size; and
- it is not possible to deduce which dietary component or combination of components effected the change in serum lipid levels.

The study provides level III-3 evidence that a modified Mediterranean diet can be effective in lowering total cholesterol and triglycerides. The results of this study concur with the findings of studies in non-transplant populations.³⁴

2 Low carbohydrate, high polyunsaturated fat diet

Shen *et al.*³⁵ conducted a pseudo-randomized controlled study examining the effect of diet on serum lipids. They designed a diet containing less than 500 mg cholesterol, less than 35% calories from fat, less than 50% calories from carbohydrate, polyunsaturated to saturated fat ratio greater than 1, limited alcohol intake. A sodium restriction was made if the transplant recipient had hypertension.

Adult kidney transplant recipients who were transplanted more than 4 months prior to the study, with stable renal function and no other condition affecting lipid metabolism, were invited to participate in the study. Of the 32 patients evaluated, nine had normolipidaemia. These formed the control group. Of the remaining patients with hyperlipidaemia, 12 volunteered for dietary treatment. These patients were instructed on the diet described above and advised to adhere to the diet for 3 months. Dietary compliance was assessed every 4 weeks. The other patients were reviewed once at the start of the study and once at the end.

After 3 months, 11 of the 12 patients following the diet had normalized HDL-cholesterol and had lost weight ($P < 0.1$). Estimations of compliance to various aspects of the diet are reported in the paper.

There was no change in the serum lipids in the hyperlipidaemic patients who had not followed the diet. Weight and serum lipids of patients in the control group remained unchanged over the 3 months.

The key limitations of this study are:

- small sample size; and
- not possible to deduce which dietary component or combination of components had the effect on serum lipid levels

However, the study provides level III evidence that a dietary restriction of fat and cholesterol may be effective in normalizing HDL-cholesterol and may lead to weight loss in adult kidney transplant recipients.

3 American Heart Association (AHA) Step One diet

Barbagallo *et al.*³⁶ looked at the effect of a modified AHA Step One diet over a 12-week period in 78 stable kidney transplant recipients.

The patients were monitored for 24 weeks prior to dietary instruction. They were then given individualized advice on the AHA Step One diet, modified to contain a higher intake of complex carbohydrates and monounsaturated fatty acids. Patients were reviewed and compliance assessed every 4 weeks.

The general trend during the 24 weeks prior to dietary intervention was an increase in serum lipid levels. After 12 weeks on the modified AHA diet, there was a significant mean reduction in total cholesterol and LDL-cholesterol, triglycerides and LDL-cholesterol to HDL-cholesterol ratio.

There were also positive shifts in the proportion of kidney transplant recipients in the 'desirable', 'borderline high risk' and 'high risk' LDL-C categories (according to US National Cholesterol Education Program criteria).

The AHA Step One and Step Two diets have been shown in non-transplant populations to be safe and efficacious in lowering LDL-cholesterol.³⁶

The key limitations of this study are:

- no control group; and
- it is not possible to deduce which dietary component or combination of components effected the change in serum lipid levels.

The study provides level IV evidence that a modified AHA diet can have favourable effects on serum lipid levels in adult kidney transplant recipients.

Weight loss

Lopes *et al.*³⁸ investigated the effect of weight loss and the AHA Step One diet on lipid profile in 23 stable kidney transplant recipients, with a body mass index of >27 at the start of the study.

The patients received monthly individualized dietary instruction on the diet, which also contained an energy restriction of 30% of estimated energy expenditure.

After 6 months of the diet, the average intake of total fat, saturated fat and cholesterol had decreased significantly ($P < 0.001$, $P < 0.01$, $P < 0.01$, respectively). The mean weight loss was 3.2 ± 2.9 kg ($P < 0.001$). Total-cholesterol decreased ($P < 0.05$). LDL-cholesterol also decreased ($P < 0.05$) but only in males.

This study provides level IV evidence to support the use of the AHA Step One diet and weight loss for reducing total- and LDL-cholesterol.

SUMMARY OF THE EVIDENCE

While dyslipidaemia is known to be a common problem after renal transplantation, there are currently few studies that consider the management of the issue in kidney transplant recipients.

The small number of studies identified have considered the effects of diet rich in wholegrain, low glycaemic index and high fibre carbohydrates as well as rich sources of vitamin E and monounsaturated fat as well as weight loss in adult kidney transplant recipients with elevated serum total cholesterol, LDL-cholesterol and triglycerides. The findings of these studies are consistent with similar studies in the general population and indicate favourable outcomes with respect to dyslipidaemia.

WHAT DO THE OTHER GUIDELINES SAY?

Kidney Disease Outcomes Quality Initiative:¹⁰

These guidelines are based on recommendations for the general population with some modifications. They do not conflict with the recommendations above.

Patients with triglycerides ≥ 500 mg/dL (≥ 5.65 mmol/L) should be treated with therapeutic lifestyle changes, including diet, weight reduction, increased physical activity, abstinence from alcohol, and treatment of hyperglycaemia (if present).

Patients with triglycerides ≥ 1000 mg/dL (≥ 11.29 mmol/L), should follow a very low fat diet ($< 15\%$ total calories), with medium-chain triglycerides and fish oils to replace some long-chain triglycerides. The diet should be used judiciously, if at all, in individuals who are malnourished.

Patients with elevated LDL-cholesterol should be treated with a diet containing $< 7\%$ energy from saturated fat, up to 10% calories from polyunsaturated fat, up to 20% calories from monounsaturated fat, giving a total fat of 25–35% of total calories. The diet should contain complex carbohydrates (50–60% of total calories) and 20–30 g fibre per day. Dietary cholesterol should be kept under 200 mg/day. For patients with LDL-cholesterol 100–129 mg/dL (2.59–3.34 mmol/L), it is reasonable to attempt dietary changes for 2–3 months before beginning drug treatment. However, kidney transplant recipients often have a number of other nutritional concerns and it is important to consult a dietitian experienced in the care of these patients.

UK Renal Association: No recommendation.

Canadian Society of Nephrology: No recommendation.

European Best Practice Guidelines:³⁹ Hyperlipidaemia risk profiles should be identified by regular screening (at least once a year) for cholesterol, HDL-cholesterol, LDL-cholesterol, triglyceride blood levels in renal transplant patients.

In renal transplant patients, hyperlipidaemia must be treated in order to keep the cholesterol/lipid levels within recommended limits according to the number of risk factors.

Management of hyperlipidaemia after transplantation should be as for the dialysis population, with, in addition, the modification of the immunosuppressive protocol when appropriate.

International Guidelines: No recommendation.

IMPLEMENTATION AND AUDIT

No recommendations.

SUGGESTIONS FOR FUTURE RESEARCH

There is a good evidence to support the use of specific dietary measures in the treatment of dyslipidaemias in the general population. There are presently no long-term dietary studies of satisfactory quality on the kidney transplant population. Well-designed, prospective, multicentre studies in kidney transplant of patients are necessary to confirm the effectiveness of the above evidence-based recommendations as well as the practice tips in normalizing serum lipid levels and improving long-term outcomes in the kidney transplant population.

CONFLICT OF INTEREST

All the above authors have no relevant financial affiliations that would cause a conflict of interest according to the conflict of interest statement set down by CARI.

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APPENDIX

Table A1 Characteristics of included studies

Study ID (author, year)	n	Study design	Setting	Participants	Intervention (experimental group)	Control group	Follow up	Comments
Stachowska <i>et al.</i> 2005	37	Randomized controlled clinical trial	Poland	Kidney transplant recipients with stable graft function	Weekly menus for 4 weeks for the modified Mediterranean diet (47% carbohydrate, 38% fat, 15% protein)	Standard low fat diet (57% carbohydrate, 26% fat, 17% protein)	6 months	Provides evidence of an effect on surrogate outcomes known to be predictive of clinical outcomes.
Shen <i>et al.</i> 1983	32	Pseudo-randomized controlled study	USA	Kidney transplant recipients (at least 4 months) with stable graft function with known lipoprotein phenotype pre-transplant	Diet – daily meal plans adequate for weight maintenance unless overweight (with a deficit of 500 kilocalories); <35% energy from fat, <500 mg chol; <50% CHO; P : S ratio >1; limited alcohol; and a sodium restriction if hypertensive.	No specified diet	3 months	Diet was designed on the basis of evidence from non-transplant populations that diets which are low in carbohydrate, high in polyunsaturated fat, low in cholesterol and low in total fat, with moderated alcohol consumption, have a beneficial effect on serum lipids levels.
Barbagallo 1999	78	Case series (no controls)	Italy	Kidney transplant recipients with stable graft function	10–12 weeks on AHA Step One Diet with higher intake of complex carbohydrates and monounsaturated fatty acids; strictly individualized with intensive counselling before starting diet and 4 weekly follow-up	N/A	10–12 weeks	After modified AHA diet, there was a significant reduction in total cholesterol and LDL-cholesterol, triglycerides and LDL-cholesterol to HDL-cholesterol ratio.
Lopes <i>et al.</i> 1999	23	Single centre prospective, pre and post test.	Spain	Kidney transplant recipients with BMI > 27	AHA Step One Diet (<30% cal from fat; <10% saturated fat, <300 mg cholesterol/day) with an energy restriction of ~30% of TEE. Monthly individualized dietary instruction provided by a clinical nutritionist	N/A	6 months	Evidence of an effect on surrogate outcomes (dietary intake, blood lipids, weight gain) that are predictive of patient-relevant outcomes (eg. CVD, diabetes, blood pressure).