Immunonutrition in Kidney and Liver Transplant Recipients

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Abstract

The immunonutrients arginine and omega-3 fatty acids decrease adverse outcomes after solid organ transplant in humans and experimental animals. Kidney transplant recipients who received daily supplements with arginine (9 g) and canola oil (30 mL) had significantly lower frequencies of complications between 30 days to 3 years than transplant recipients who did not receive supplements. In another study in kidney transplant recipients, arginine combined with either canola oil or fish oil was safe, effective, and provided good protection against rejection in patients who had steroid-free immunosuppression. In the 27 patients (50%) who had omega-3 index (percent omega-3 component of all fatty acids in red blood cell membranes) > 6 there was no acute rejection by 1 year after transplant; in 27 patients who had omega-3 index < 6, there were 5 patients (19%) who had acute rejection \( (P \leq .01) \). No studies are available in liver transplant patients that have provided adequate doses or duration of immunonutrients. A prospective, randomized, double-blind clinical trial using immunonutrients is proposed for patients having primary liver transplant. In summary, immunonutrition in kidney transplant recipients with high doses of oral arginine and omega-3 fatty acids is effective, safe, and inexpensive, and may decrease the frequency of complications such as rejection, infection, new onset diabetes and cardiovascular disease. Further study with similar protocols in liver transplant recipients is justified.

Key words: Arginine, Complications, Fish oil, Immunosuppression

Introduction

A dietary supplement containing high levels of protein, additional arginine, and fish oil, developed in the 1980s (Impact, Sandoz Nutrition, Minneapolis, MN, USA), may reduce the frequency of complications in surgical patients such as wound infections, prolonged hospital stay, and systemic inflammatory response syndrome.\(^1\)-\(^4\) Rats that were given this supplement as the only source of nutrition and low-dose cyclosporine for 14 days achieved functional transplant tolerance, with cardiac allograft survival > 200 days to 1 year.\(^5\) Experiments with lower doses of cyclosporine showed that arginine and fish oil independently improved cardiac allograft survival in rats.\(^6\) Other types of lipids such as alpha linoleic acid, oleic acid, and canola oil (that contained combinations of alpha linoleic acid and oleic acid) also were effective.\(^7\) Arginine was the most effective amino acid among those studied.\(^8\)

Clinical Studies Using Immunonutrients

Based on the results of animal studies, a prospective, randomized clinical trial was performed in 147 kidney transplant recipients who received daily supplements with arginine (9 g) and canola oil (30 mL) or no supplements (control).\(^9\) The dietary supplements were not expected to affect cellular function in the first month because 1 month typically is required for sufficient amounts of lipids to be incorporated into cell membranes; there was no difference observed between the 2 patient groups
during the first 30 days. However, from 30 days to 3 years after transplant, there were significantly lower frequencies of complications in the supplemented than control groups (Table 1). There were no episodes of acute rejection after the first year in the patients who received supplements. Although the frequency of positive blood cultures was lower in supplemented than control patients, there were no differences between the patients in respiratory, urinary tract, or cytomegalovirus infections.

Table 1. Relation Between Supplemental Arginine and Canola Oil and Complications of Kidney Transplant

<table>
<thead>
<tr>
<th>Complication</th>
<th>Supplemented Patients (n=76)</th>
<th>Control Patients (n=71)</th>
<th>P value</th>
<th>Decrease (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First rejection†</td>
<td>5.4%</td>
<td>23.7%</td>
<td>.01</td>
<td>77%</td>
</tr>
<tr>
<td>Calcineurin inhibitor toxicity†</td>
<td>9.2%</td>
<td>35.3%</td>
<td>.003</td>
<td>74%</td>
</tr>
<tr>
<td>Positive blood cultures</td>
<td>6.5%</td>
<td>18.9%</td>
<td>.05</td>
<td>66%</td>
</tr>
<tr>
<td>New-onset diabetes mellitus</td>
<td>2.3%</td>
<td>14.5%</td>
<td>.004</td>
<td>84%</td>
</tr>
<tr>
<td>Cardiac events‡</td>
<td>4.0%</td>
<td>17.1%</td>
<td>.05</td>
<td>73%</td>
</tr>
</tbody>
</table>

*Time of complication, 30 days to 3 years after transplant. Data from Alexander (2005). 11
†Proven with biopsy.
‡Cardiac events included myocardial infarction, death from cardiac disease, angioplasty, placement of a stent, coronary artery bypass graft surgery, and hospitalization for major peripheral vascular disease.

Immunonutrients and immunosuppression after transplant

Steroids and calcineurin inhibitors are important immunosuppressive drugs but they have numerous adverse events. A clinical study evaluated immunonutrients as a replacement of immunosuppressive drugs after kidney transplant, with steroid-free induction and maintenance, early withdrawal of calcineurin inhibitors, and discontinuation of mycophenolate mofetil (Table 2). 10 Cyclosporine was discontinued by 4 to 6 months in subgroups 2 to 4. Most patients did not have rejection at 1 year (86%) and 3 years (79%) and no patient in subgroup 4 receiving fish oil for one year had a rejection. No kidney graft was lost to acute rejection, and steroids were allowed to treat acute rejection. Most patients who were alive at the end of the study were steroid-free (90%) and most were not receiving calcineurin inhibitors (87%). Many patients who had a functioning kidney at 3 years (> 50% patients) were receiving rapamycin and nutrients only. Therefore, arginine combined with either canola oil or fish oil is safe and effective and may provide good protection against rejection.

Polynsaturated fatty acids and ornithine in kidney transplant

Blood samples were drawn from 54 patients, including patients from the previous 2 studies, from 30 to 365 days after kidney transplant; these patients received arginine and fish oil, arginine and canola oil, or no supplements. 11 Amino acid profiles were performed on plasma, and fatty acid profiles were performed on red blood cell membranes using gas chromatography and mass spectroscopy. In the 27 patients (50%) who had omega-3 index (percent omega-3 component of all fatty acids in red blood cell membranes) > 6, there was no acute rejection by 1 year after transplant. However, in the 27 patients who had omega-3 index < 6, there were 5 patients (19%) who had acute rejection (P ≤ .01) (Figure 1). 11 In cell membranes, omega-6 fatty acid levels are inversely proportional to omega-3 fatty acids.

Table 2. Target Immunonutrients and Immunosuppression in a Steroid-free Protocol After Kidney Transplant* (Target = Amount to be Given)

<table>
<thead>
<tr>
<th>Target Immunosuppression</th>
<th>Subgroup 1 (n=18)</th>
<th>Subgroup 2 (n=45)</th>
<th>Subgroup 3 (n=20)</th>
<th>Subgroup 4 (n=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thymoglobulin</td>
<td>1.5 mg/kg, 3 doses</td>
<td>Same</td>
<td>Same</td>
<td>Same</td>
</tr>
<tr>
<td>Rapamycin</td>
<td>2 mg/d (target level: 0 to 90 d: 9 to 15 ng/dl; &gt; 90 d: 8 to 12 ng/dl)</td>
<td>Same</td>
<td>Same</td>
<td>Same</td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
<td>0 to 9 mo: 1000 mg twice/d</td>
<td>9 to 12 mo: 750 mg twice/d</td>
<td>12 to 24 mo: 500 mg twice/d</td>
<td>24 mo: discontinued</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>4 mg/kg/d (target level: 0 to 90 d: 200 mg/mL; &gt; 90 d: 150 mg/mL; 181 to 365 d: 100 mg/mL)</td>
<td>2 mg/kg/d (target level: 0 to 180 d: 100 mg/mL; &gt; 180 d, discontinued)</td>
<td>1 mg/kg/d (target level: none specified; &gt; 4 mo, discontinued)</td>
<td>2 mg/kg/d (target level: 0 to 180 d: 100 mg/mL; &gt; 180 d, discontinued)</td>
</tr>
<tr>
<td>Arginine</td>
<td>4.5 g twice/d/d</td>
<td>Same</td>
<td>Same</td>
<td>Same</td>
</tr>
</tbody>
</table>
| Canola oil               | 15 mL twice/d    | Same              | Same              | 0                 
| Fish oil†                | 0                 | 0                 | 0                 | 4 to 5 packets     |

*N=96 patients. Adapted from Alexander (2006). 11
†Omega-3 fish oil supplement (Coromega, Carlsbad, CA, USA): 4 to 5 packets; each packet contained docosahexaenoic acid (190 mg) and eicosapentaenoic acid (290 mg).
levels. Therefore, the patients who had low levels of omega-6 fatty acids did not have rejection, but patients who had high levels of omega-6 fatty acids had a significantly greater frequency of rejection (20%) (Figure 1). High levels of ornithine were significantly associated with prevention of new-onset diabetes mellitus, but there was no relation between serum arginine level and frequency of new-onset diabetes mellitus (Figure 2).\textsuperscript{11}

**Myeloid-derived suppressor cells, arginine, and omega-3 fatty acids**

The biological functions of myeloid-derived suppressor cells and regulatory T cells have been reviewed, including interactions of cytokines, prostaglandins, and other mediators.\textsuperscript{12} Myeloid-derived suppressor cells and regulatory T cells may prolong allograft survival, induce tolerance and prevent the development of diabetes. The generation of myeloid-derived suppressor cells and regulatory T cells during the combined administration of large amounts of arginine and omega-3 fatty acids may inhibit immune responses. In diabetic patients who had islet cell transplant, myeloid-derived suppressor cells cotransplanted with the islet allografts protected the islet allografts without immunosuppressive drugs and caused marked expansion of regulatory T cells.\textsuperscript{13}

**Immunonutrition in liver transplant**

The use of an oral dietary supplement containing high levels of protein, additional arginine, and fish oil (before transplant and 5 days after transplant: 600 mL/d) was evaluated after liver transplant (supplement, 15 patients; control patients who had typical diet with no supplement, 17 patients).\textsuperscript{14} The supplement was well tolerated, but there was no difference between groups in frequency of rejection. In this study, the doses of arginine and omega-3 fatty acids were not sufficient to suppress inflammatory responses and the supplements were stopped too early after transplant to observe an effect. Another study by the same researchers did not show any beneficial effects.\textsuperscript{15} No studies are available in liver transplant patients that have provided adequate doses or duration of immunonutrients.

**Figure 1.** Relation Between Omega-3 and Omega-6 Fatty Acids and Acute Rejection After Kidney Transplant

(A) Omega-3 index was the percent omega-3 component of all fatty acids in red blood cell membranes. (B) Total omega-6 was the omega-6 concentration in red blood cell membranes. Reprinted with permission from Başkent University.\textsuperscript{11}

**Figure 2.** Relation Between Plasma Ornithine (A) and Arginine (B) Levels and New-Onset Diabetes Mellitus After Kidney Transplant

*Abbreviations:* ARG, arginine; ORN, ornithine

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Proposed Study for Liver Transplant Patients

A prospective, randomized, double-blind clinical trial using immunonutrients is proposed for patients having primary liver transplant. When patients can tolerate oral intake after liver transplant, study patients will take arginine (4.5 g twice daily) and fish oil supplements (1 g capsules; 3 capsules in the morning and 4 capsules in the evening) with food for ≥ 1 year. The control group will receive no supplements and may receive a placebo. Study and control patients will receive similar immunosuppressive drugs. The primary outcome will be biopsy-proven rejection. The hypothesis is that patients who have supplements will have decreased frequency of rejection. Secondary outcomes will include frequency of new-onset diabetes mellitus, cardiovascular events, and infections; degree of fatty liver; and overall costs.

References