

# Immunologic Aspects of Perioperative Nutrition

L. Andersen<sup>1,\*</sup>, M. Rasmussen<sup>2</sup> and R. Beier-Holgersen<sup>3</sup>

<sup>1</sup>Department of Gastrointestinal Surgery, Sjaellands University Hospital Koege, Denmark

<sup>2</sup>Department of Gastrointestinal Surgery, Holbaek Hospital, Denmark

<sup>3</sup>Department of Gastrointestinal Surgery, Nordsjaellands Hospital, Denmark

**Abstract:** Nutrition has proven to be of great importance for the postoperative clinical outcome. Several studies have shown that infectious complications in the surgical patient, are reduced by pre- or postoperative nourishment. We discuss cellular immunity in relation to both enteral and parenteral nutrition and present an updated literature study of current evidence. The aim of this paper is to give an overview of studies, that compare different immunological parameters in the surgical patient being nourished either enterally or parenterally.

**Keywords:** Parenteral nutrition, enteral nutrition, cellular immune response, surgery.

## INTRODUCTION

During the postoperative period, nutrition has proven to be of great importance for the postoperative clinical outcome. Several studies have shown that by selective nourishing of patients undergoing surgery, infectious complications are reduced [1-3].

However, the optimal pathway (either preoperatively or postoperatively) to nourish patients is unknown. Some studies suggest that nourishing patients parenterally does not significantly reduce infections postoperatively [1, 4, 5].

Studies directly comparing enteral and parenteral postoperative nutrition have shown that enteral nutrition significantly reduced infectious complications compared with parenteral nutrition [5]. The immunological reason for this presumed effect is not well understood.

The aim of this paper is to give an updated overview of studies, that compare specific immunological parameters of patients being nourished enterally and parenterally, pre- and postoperatively.

## METHODS

We conducted a literature search in PubMed by 2 independent investigators focusing on cellular immune response parameters, the surgical patient and the perioperative period. The search was divided into enteral and parenteral nutrition.

The primary aim was to investigate evidence for changes in immunologic parameters dependent on different routes of nutrition (enteral or parenteral). MeSH terms used were: "enteral nutrition", "parenteral nutrition", "cellular immune response", "surgery".

## Cellular Immunity, Terminology

Cellular immunity is divided into the innate (non-specific) immune system consisting of macrophages and other cells doing phagocytosis, and the adaptive (specific) immune system composed of lymphocytes.

In literature, measurements of cellular immunity activity are often described according to the percentage of different "clusters of differentiation" (CD) eg. CD3+, CD4+, CD3- present in blood (Table 1). An alternative presentation is by subtype in the major-histocompatibility complex molecule (MHC II). MHC II is divided in different human leucocyte antigens, ("HLAs") such as HLA-DR.

**Table 1: Common Immunologic Parameters Expressing Cellular Immune Activity**

Name	Immune function
CD3+	Pan T-cell
CD4+	Helper cell
CD8+	Cytotoxic cell
CD3-	NK cell
CD16+	NK cell
CD56+	NK cell
CD69+	Activated T-cell and NK cell
IL-6	Proinflammatory cytokine, B-cell activator
IL-10	Anti-inflammatory cytokine, T-cell production

\*Address correspondence to this author at the Department of Gastrointestinal Surgery, Sjaellands University Hospital Koege, Lykkebaekvej 1, 4600 Koege, Denmark; Tel: +4547323011; Fax: +4556631569; E-mail: lene\_andersen\_@hotmail.com

In much of the literature, the number of cell changes over time is expressed as a change in percentage. Unfortunately, many authors do not indicate the actual number of lymphocytes. A direct comparison of lymphocyte count and the immunological markers change over time is therefore often impossible. To compare percentage values at different times without an actual lymphocyte count in relation to these sub-populations is not possible. However, comparison is possible by usage of ratios, e.g. the CD4/CD8 ratio.

### Enteral Nutrition and Cellular Immunity

In a randomized controlled trial including 60 patients, Beier-Holgersen and Brandstrup [6] compared 2 different postoperative enteral nutritional regimes (food vs. no food) and immunologic response. A significantly larger number of lymphocytes, monocytes, NK cells and also activated T cells (CD69+), were found in the food group when measured postoperatively compared to the no food group. HLA-DR activated cells significantly increased from the third post-operative day onwards, compared to the "no food" group. The results indicate that cellular immunity activity was significantly higher in the food group.

Sultan *et al.* [7] compared a pre- and postoperative enteral nutrition regime in a group receiving postoperative enteral feeding (based solely on the clinical consultants' preference). The patients were randomized to enteral nutrition with or without supplemented omega-3 fatty acids. 195 patients undergoing oesophago-gastric cancer surgery were included. The results did not show any significant effect on either immune parameters measured as HLA-DR expression in leucocytes or on clinical outcome.

In a prospective study Li *et al.* [8] compared postoperative enteral and parenteral nutrition in 400 patients after radical gastrectomy. The enteral nutrition group regained preoperative levels of CD4, CD4/CD8 and NK cells faster postoperatively compared to the parenteral nutrition group where levels were significantly lower. There was no difference in clinical outcome.

Takagi K *et al.* [9] compared perioperative enteral and parenteral nutrition in a retrospective study in 29 patients undergoing esophagectomy. IL-6, IL-10 as well as endotoxins (part of the cell wall of gram-negative bacteria) were measured. The postoperative endotoxin concentration in sera was significantly lower in the group receiving enteral nutrition. Based on these results the authors suggest that perioperative enteral

nutrition provides better regulation of inflammatory cytokine response and may contribute to less immunosuppression after major surgery than parenteral nutrition.

Suzuki D *et al.* [10] studied 30 patients undergoing pancreaticoduodenectomy, in a prospective study. 3 groups received enteral nutrition pre- and postoperatively, enteral nutrition postoperatively or parenteral nutrition postoperatively. T cell and NK cell activity were significantly higher in the group receiving enteral nutrition pre- and postoperatively compared to the other groups, as well as other measured immunologic parameters. The authors concluded that perioperative nutrition reduces the rate of postoperative infections.

### Parenteral Nutrition and Cellular Immunity

Furukawa *et al.* [11] randomized 36 patients undergoing abdominal surgery to parenteral nutrition with or without added soybean emulsion. Immunologic parameters measured were IL-6 and T-cell/NK cell proliferation. The addition of soybean emulsion increased the stress response and repressed the cellular immune response in already severely stressed patients. The study did not include a group receiving "no food" compared to parenteral nutrition.

In a prospective randomized study by Dionigi P DR *et al.* [12], 15 malnourished patients undergoing operations for upper GI-cancer were randomized to receive parenteral nutrition with either intralipid or glucose postoperatively. The results showed that T- and B-lymphocyte count, chemotaxis and granulocyte adherence were depressed in the group receiving parenteral nutrition with added glucose. The authors concluded that postoperative infections were less severe in patients receiving intralipid.

Long *et al.* [13] compared 60 patients undergoing esophageal cancer surgery in a prospective study, who received parenteral nutrition with or without omega-3-polyunsaturated fatty acids ( $\omega$ 3-PUFAs). Procalcitonin, an inflammatory marker and CD4+/CD8+ ratios were determined perioperatively. In the group receiving  $\omega$ 3-PUFAs the CD4+/CD8+ ratio were higher and procalcitonin lower. The authors thus suggest that  $\omega$ 3-PUFAs can reduce inflammation and improve immune function postoperatively.

A prospective randomized (single blinded) study by Yao *et al.* [14] included 61 patients undergoing surgery

for bowel obstruction due to chronic radiation enteritis. The patients were randomized to parenteral nutrition alone or supplemented with glutamine dipeptide. Outcomes were serum glutamine level and the CD4/CD8-positive T-lymphocytes ratio. The group receiving glutamine was less prone to developing fever, but no other clinical difference were found. The CD4/CD8-positive T-lymphocytes ratios rose in both groups, however with significant higher ratio measured in the glutamine supplemented group.

A prospective single blinded trial by JM Asprer *et al.* [15] randomized 34 malnourished patients undergoing elective abdominal surgery, to preoperative parenteral supplementation with or without added glutamine dipeptide. Primary outcomes were several different "immune indices" measured as change in cell count. In the group receiving glutamine supplementation an increase in immune cells were found compared to no change in the group receiving only parenteral nutrition. The clinical outcome between groups were similar and the effect on immune cells were not sustained after glutamine dipeptide supplementation stopped.

## DISCUSSION

The literature concerning effect of enteral or parenteral nutrition on cellular immunologic parameters is sparse. Studies include few patients, conclusions are drawn on different immune cell lines and seldom with measurable clinical difference. Study designs vary considerable e.g. feeding routes and nutritional components. A specific connection between varying immunologic parameters and clinical outcome is yet to be identified.

Many studies show a measurable percentage difference between nutritional intervention by the usage of subpopulations of lymphocytes, without known lymphocyte count. This does not describe the immunological aspects correctly (15,16,18,19,20).

For the patient undergoing major surgery, nutritional status betters clinical outcome [1-3] but the immunologic parameters that correspond to clinical results and nutritional regime is unknown. There seems to be a larger effect of enteral nutrition on immunological parameters then parenteral nutrition (12, 13, 14).

The inherent challenge of supplying sufficient nutrition to patients undergoing surgery especially to the GI tract also warrants further research because

nutritional absorption naturally depends on mucosal integrity and gastrointestinal continuity [16].

Further studies must identify both the specific immunologic parameters that correlate to relevant clinical outcome and measure effect in different routes of feeding.

## REFERENCES

- [1] Mochizuki H, Togo S, Tanaka K, Endo I, Shimada H. Early enteral nutrition after hepatectomy to prevent postoperative infection. *Hepatogastroenterology* 2000; 47(35): 1407-1410.
- [2] Okamoto K, Fukatsu K, Hashiguchi Y, Ueno H, Shinto E, Moriya T, Saitoh D, Yamamoto J, Hase K. Lack of preoperative enteral nutrition reduces gut-associated lymphoid cell numbers in colon cancer patients: a possible mechanism underlying increased postoperative infectious complications during parenteral nutrition. *Ann Surg* 2013; 258(6): 1059-1064.  
<http://dx.doi.org/10.1097/SLA.0b013e31827a0e05>
- [3] Beier-Holgersen R, Boesby S. Influence of postoperative enteral nutrition on postsurgical infections. *Gut* 1996; 39(6): 833-835.  
<http://dx.doi.org/10.1136/gut.39.6.833>
- [4] Pham KN, Schwartz LW, Garg T, Langenstroer P, Guralnick ML, See WA, O'Connor RC. Immediate total parenteral nutrition after radical cystectomy and urinary diversion. *WMJ* 2014; 113(1): 20-23.
- [5] Bozzetti F, Braga M, Gianotti L, Gavazzi C, Mariani L. Postoperative enteral versus parenteral nutrition in malnourished patients with gastrointestinal cancer: a randomised multicentre trial. *Lancet* 2001; 358(9292): 1487-1492.  
[http://dx.doi.org/10.1016/S0140-6736\(01\)06578-3](http://dx.doi.org/10.1016/S0140-6736(01)06578-3)
- [6] Beier-Holgersen R, Brandstrup B. Influence of postoperative enteral nutrition on cellular immunity. A random double-blinded placebo controlled clinical trial. *Int J Colorectal Dis* 2012; 27(4): 513-520.  
<http://dx.doi.org/10.1007/s00384-011-1335-0>
- [7] Sultan J, Griffin SM, Di Franco F, Kirby JA, Shenton BK, Seal CJ, Davis P, Viswanath YK, Preston SR, Hayes N. Randomized clinical trial of omega-3 fatty acid-supplemented enteral nutrition versus standard enteral nutrition in patients undergoing oesophagogastric cancer surgery. *Br J Surg* 2012; 99(3): 346-355.  
<http://dx.doi.org/10.1002/bjs.7799>
- [8] Li B, Liu HY, Guo SH, Sun P, Gong FM, Jia BQ. The postoperative clinical outcomes and safety of early enteral nutrition in operated gastric cancer patients. *J BUON* 2015; 20(2): 468-472.  
<http://dx.doi.org/10.1016/j.bone.2015.08.017>
- [9] Takagi K, Yamamori H, Toyoda Y, Nakajima N, Tashiro T. Modulating effects of the feeding route on stress response and endotoxin translocation in severely stressed patients receiving thoracic esophagectomy. *Nutrition* 2000; 16(5): 355-360.  
[http://dx.doi.org/10.1016/S0899-9007\(00\)00231-8](http://dx.doi.org/10.1016/S0899-9007(00)00231-8)
- [10] Suzuki D, Furukawa K, Kimura F, Shimizu H, Yoshidome H, Ohtsuka M, Kato A, Yoshitomi H, Miyazaki M. Effects of perioperative immunonutrition on cell-mediated immunity, T helper type 1 (Th1)/Th2 differentiation, and Th17 response after pancreaticoduodenectomy. *Surgery* 2010; 148(3): 573-581.  
<http://dx.doi.org/10.1016/j.surg.2010.01.017>
- [11] Furukawa K, Yamamori H, Takagi K, Hayashi N, Suzuki R, Nakajima N, Tashiro T. Influences of soybean oil emulsion on

- stress response and cell-mediated immune function in moderately or severely stressed patients. *Nutrition* 2002; 18(3): 235-240.  
[http://dx.doi.org/10.1016/S0899-9007\(01\)00784-5](http://dx.doi.org/10.1016/S0899-9007(01)00784-5)
- [12] Dionigi P DR, Prati U, Pavesi F, Jemos V, Nazari S. Effect of intralipid on some immunological parameters and leukocyte functions in patients with esophageal and gastric cancer. *Clin Nutr* 1985(4): 229-234.  
[http://dx.doi.org/10.1016/0261-5614\(85\)90008-1](http://dx.doi.org/10.1016/0261-5614(85)90008-1)
- [13] Long H, Yang H, Lin Y, Situ D, Liu W. Fish oil-supplemented parenteral nutrition in patients following esophageal cancer surgery: effect on inflammation and immune function. *Nutr Cancer* 2013; 65(1): 71-75.  
<http://dx.doi.org/10.1080/01635581.2013.741761>
- [14] Yao D, Zheng L, Wang J, Guo M, Yin J, Li Y. Perioperative Alanyl-Glutamine-Supplemented Parenteral Nutrition in Chronic Radiation Enteritis Patients With Surgical Intestinal Obstruction: A Prospective, Randomized, Controlled Study. *Nutr Clin Pract* 2015.
- [15] Asprer JM, *et al.* Effect on immune indices of preoperative intravenous glutamine dipeptide supplementation in malnourished abdominal surgery patients in the preoperative and postoperative periods. *Nutrition* 2009; 25(9): 920-5.  
<http://dx.doi.org/10.1016/j.nut.2009.01.014>
- [16] Mukhopadhyay A, *et al.* Can Postoperative Nutrition be Favourably Maintained by Oral Diet in Patients with Emergency Temporary Ileostomy? A Tertiary Hospital Based Study. *J Clin Diagn Res* 2015; 9(12): PC04-8.  
<http://dx.doi.org/10.7860/jcdr/2015/15220.6879>

---

Received on 17-05-2016

Accepted on 19-07-2016

Published on 07-10-2016

[DOI: http://dx.doi.org/10.6000/1929-5634.2016.05.03.1](http://dx.doi.org/10.6000/1929-5634.2016.05.03.1)