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Perioperative Immunonutrition in Patients with Colorectal Cancer

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Abstract

Colorectal Cancer (CRC) is one of the most diagnosed cancers among men and women worldwide. The incidence of CRC has been rising due to risk factors such as a sedentary, obesity, high fat diet and unhealthy lifestyle. Surgical treatment for excision of the primary tumor represents 80% of all CRC treatments. For this procedure, patients need to be prepared to withstand surgical aggression, regardless of their nutritional status. To this end, studies have demonstrated the use of nutritional formulas with Immunonutrients (IN), a mix of omega-3 fatty acids, glutamine, arginine, and nucleotides, which modulate the surgical inflammatory response, reducing the risk of infectious complications (i.e., surgical site infection) and non-infectious (i.e., anastomotic dehiscence or enteric fistulas). In addition, IN has been reducing hospital length of stay (LOS) and overall hospital costs. Recent studies have shown that these IN formulations have better results in CRC patients if given 5-7 days before surgery and restarted after surgery for an additional 5-7 days or until patients are able to resume oral intake, covering at least 60% of their requirements.

Keywords: Immunonutrition; Surgery; Colorectal cancer; Perioperative care.

Introduction

Colorectal cancer (CRC) is the third and second most diagnosed cancer in males and females, respectively [1]. CRC accounts for approximately 10% of all annually diagnosed cancers and cancer-related deaths worldwide because it is ranked second in both sexes [1].

In women, the incidence and mortality are approximately 25% lower than in men [2]. CRC incidence has been steadily rising worldwide, especially in developing countries that are adopting the “western” way of life. Sedentary lifestyle, obesity, red meat consumption, alcohol, and tobacco are considered the risk factors behind the growth of CRC [3] according to demonstrated in Figure 1.

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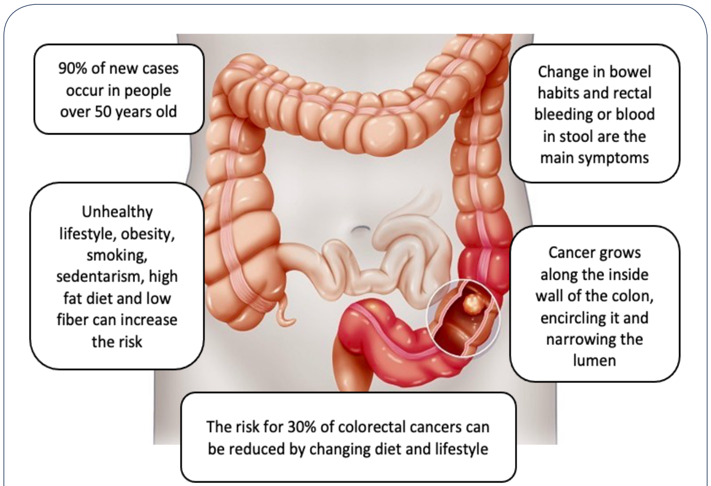

Figure 1: Epidemiology and risk factors for colorectal cancer.

The surgery is the most common and an essential part of the treatment in CRC [4]. Surgery for excision of the primary tumor is undertaken in 80% of patients diagnosed. However, the patients with CRC need to be prepared for the entire surgery journey, from preoperative care to the late postoperative [5]. Perioperative care has been optimized by a multi-interventional enhanced recovery programme, trying to keep physiology and daily functioning to healthy conditions [6,7].

Nevertheless, complications continue to occur such as surgical site infection, anastomotic leak, intra-abdominal abscess, enteric fistula, bleeding, and postoperative bowel obstruction [4,8,9]. The timely and efficient identification of these complications is vital for effective clinical management of these patients to reduce their morbidity and mortality. Postoperative complications significantly affect the short-term outcomes, the length of hospital stay (LOS) and the costs [8,10].

These patients with CRC usually have nutritional status changes and a low-grade inflammatory process. It is worth remembering that the cancer growth is associated with an exaggerated systemic inflammatory response, which can induce insulin resistance, protein hypercatabolism, and lipolysis, leading to the loss of muscle protein and body fat. These conditions may cause various cancer-related symptoms such as generalized fatigue, pain, nausea, or anorexia, which result in poorer nutritional status [6,11,12].

The positive impact of perioperative nutritional support as an adjunct to perioperative care in major surgery has been repeatedly demonstrated [13]. However, the timing and composition of specialized nutritional formulations are still unknown to many healthcare professionals. While there is a consensus that surgical patients need early nutritional support to counterbalance deficits more effectively, as postoperative catabolism is linked to inactivity, prolonged recovery, and fatigue, especially in patients with postoperative complications [14].

Specific nutrients with immunological and pharmacological effects, when consumed in amounts above the daily requirement, are referred to as immune-enhancing nutrients or immunonutrients [15,16]. In more recent times, the use of immunonutrition (IN) containing immune enhancing nutrients such as glutamine, omega-3 fatty acids, arginine, and nucleotides to modulate metabolism and immune responses in surgical patients has been proposed [15-17].

Immunonutrients

Omega-3 fatty acids

Fish oil derived omega-3 fatty acids displacing the arachidonic acid of the cell membrane of immune cells attenuate the production of inflammatory prostaglandins and prostacyclins and reduce the cytotoxicity of inflammatory cells. Fish oil derived fatty acids: Eicosapentanoic Acid (EPA) and Docohexanoic Acid (DHA) are the precursors of resolvins, shown to reduce cellular inflammation by inhibiting the transportation of inflammatory cells and mediators to the site of inflammation [18].

DHA and EPA appear to act via overlapping, as well as distinct, mechanisms of action, modifying cellular function to benefit overall health and wellbeing, as well as to reduce the risk and severity of disease. It is their membrane-mediated mechanisms that are most well established and understood and it is considered that through alterations at the membrane level in different cell and tissue types, DHA and EPA play an important role in cell signaling, gene expression and lipid mediator production [19].

The increased intake of EPA and DHA results in enhanced appearance of those fatty acids in the membrane phospholipids of cells involved in inflammation. Cell membranes become more fluid, affecting the behavior of several membrane proteins, including their aggregation into signaling platforms, so-called lipid rafts. As a result, transmission of inflammatory signals within cells, for example from lipopolysaccharide or saturated fatty acids, becomes blunted, resulting in reduced activation of pro-inflammatory transcription factors like nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) [11,16].

Thus, though these effects are initiated at the cell membrane level, omega-3 fatty acids can affect multiple inflammatory mediators and their anti-inflammatory actions could be wide-ranging as a result. The increase of EPA and DHA in the membranes of inflammatory cells is that they partially replace the omega-6 fatty acids (arachidonic acid). Arachidonic acid is the usual substrate for cyclooxygenase, lipoxygenase, and cytochrome P450 enzymes producing eicosanoids; these eicosanoids (e.g., prostaglandin E2, leukotriene B4) are recognized mediators of inflammation. Therefore, through the EPA- and DHA-mediated decrease in arachidonic acid availability, production of these inflammatory eicosanoids is decreased [15,18].

Arginine

Arginine (2-amino-5-guanidinovaleric acid) is an alpha-amino acid that is involved in several critical processes in human health and disease. Aside from being the nitrogen source for nitric oxide generated by endothelial and immune cells in vasodilatory and host-defense mechanisms, respectively, arginine is also used to synthesize creatine to meet muscle metabolic demands as well as urea synthesis to maintain whole-body nitrogen balance [20,21]. Additionally, arginine stimulates protein translation and polyamine synthesis – anabolic and proliferative functions that become unregulated in cells after malignant transformation. This conditionally essential amino acid arginine can function as a precursor of proline and polyamines, which are essential for tissue repair and wound healing [17,20-22].

Arginine is also crucial for the integrity and function of immune cells. In addition, arginine is an important immune-modulating nutrient as a precursor of nitric oxide synthesis. Studies have shown that arginine deficiency occurs because of surgical injury [7,17,23].

Glutamine

Glutamine provides fuel for rapidly dividing cells (particularly lymphocytes and enterocytes) as well as the epithelial cells of the intestines. Glutamine maintains gut barrier function and is a precursor for the endogenous antioxidant glutathione. It plays an important role in nitrogen transport within the body and serves as a substrate for renal ammonia genesis [21,24].

Glutamine induces the expression of heat shock proteins and stimulates nucleotide synthesis. Signaling mediators such as extracellular signal-regulated protein kinases that regulate cell differentiation are activated by glutamine. Glutamine contributes to mucin formation and intestinal surface integrity by mediating the synthesis of N-acetylglucosamine and N-acetylgalactosamine [16].

Nucleotides

Nucleotides have been reportedly beneficial since they positively influence lipid metabolism, immunity, and tissue growth, development, and repair. Rapidly proliferating tissues, such as the immune system or the intestine are not able to fulfil the needs of cell nucleotides exclusively by de novo synthesis and they preferentially utilize the salvage pathway recovering nucleosides and nucleobases from blood and diet [25].

Dietary nucleotides modulate immune function, improve intestinal healing and trophic effects on the intestine. Nucleotide supplementation has also been shown to promote some aspects of tissue recovery from ischemia/reperfusion injury or radical resection. The intestine and liver possess powerful homeostatic mechanisms which degrade intake of purines and pyrimidines (i.e., salvage) and replace it with de novo synthesized output [26].

Previously, nucleotides have been proposed as being conditionally essential nutrients that provide an adequate supply of purines and pyrimidines for nucleic acid synthesis in the stressed patient such as cancer patients undergoing surgery [25,26].

Discussion

It has long been known that in any surgical procedure, the body reacts with the release of stress hormones, such as cortisol, catecholamines and glucagon. Those hormones are released quite quickly and cause changes to metabolism, by mobilizing substrates from all energy storages — including glucose from glycogen, fat from fat deposits, and protein mainly from muscles [27]. At the same time, the inflammatory system is also activated in injuries. Therefore, cytokines are released, among which, tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6) have been identified in the metabolic responses and increased production of acute-phase proteins [17].

Metabolic response to surgery causes hyperinflammation, oxidative stress, and immune impairment, which increase the risk of postoperative infections [28]. Therefore, the aim of IN is to modulate the metabolic response after surgery by using specific nutritional substrates with metabolic effects in patients with high risk to develop postoperative infections, regardless of baseline nutritional status [5,29,30].

Multiple studies and meta-analyses have suggested some benefit to IN supplements in patients with CRC [31,32]. These studies have often included pre- and post-operative regimens and have utilized inconsistent controls ranging from standard non-supplemented oral diets to high-quality isonitrogenous controls [32-34].

Braga et al. demonstrated that IN supplementation induced an immune response, increased intestinal microperfusion and oxygenation [22]. Waitzberg et al. showed the beneficial effects of IN supplementation on clinical outcomes in elective surgery patients with significant reductions in infectious complications and LOS. Their analysis of postoperative outcomes in surgical patients suggests that the best outcomes were observed when IN supplementation was supplemented during the preoperative period, generally 0.5–1.0 l/day for 5–7 days before surgery [28].

Some studies with perioperative IN have also shown benefits for non-malnourished patients and in laparoscopic surgery, which theoretically minimizes an inflammatory response. Moya et al. showed that IN supplements reduce surgical site infection even in normo-nourished patients and with the laparoscopic approach. In that study, receiving IN preoperatively and postoperatively had fewer surgical site infections than those who received dietary advice and reduced the rate of surgical site infection [34,35].

According to the European Society of Parenteral and Enteral Nutrition (ESPEN) guidelines for surgery, based on a grade A level of evidence, IN is already indicated for all patients operated for digestive cancer 5 to 7 days prior to surgery, regardless the patient nutritional status (Figure 2). The IN should be continued in the postoperative phase in patients for 5 to 7 days or until patients are able to resume oral intake, covering at least 60% of their requirements [36,37].

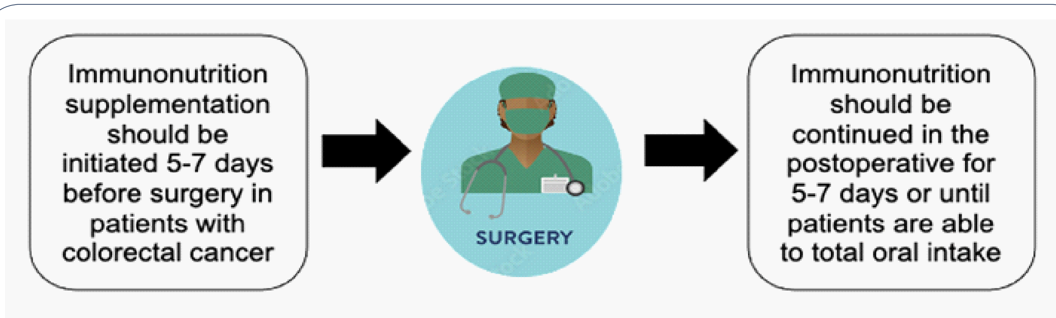

Figure 2: Perioperative immunonutrition regimen in patients with colorectal cancer.

Conclusion

As a result of advances in medicine, surgical procedures are generally less invasive and there is a great tendency to prepare the patients before the surgery, or even wait until the patient is viable to withstand the surgical aggression. It is worth remembering that immunity is compromised due to tissue stress ischemia and reperfusion combined with hemorrhage and transfusion. In addition, the colorectal cancer surgical patient it at risk of the common and costly postoperative complications of elective surgery, such as anastomotic fistula or dehiscence.

In this context, perioperative IN (omega-3 fatty acids, arginine, glutamine and nucleotides) appears with the proposal to modulate the surgical inflammatory response, mitigating the risks that involve especially patients with cancer. The results show lower rates of infectious and non-infectious complications and shorter LOS, ensuring a better quality of life for the patients.

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