Nutritional Aspects of Gastrointestinal Wound Healing

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Significance: Although the wound healing cascade is similar in many tissues, in the gastrointestinal tract mucosal healing is critical for processes such as inflammatory bowel disease and ulcers and healing of the mucosa, submucosa, and serosal layers is needed for surgical anastomoses and for enterocutaneous fistula. Failure of wound healing can result in complications including infection, prolonged hospitalization, critical illness, organ failure, readmission, new or worsening enterocutaneous fistula, and even death.

Recent Advances: Recent advances are relevant for the role of specific micronutrients, such as vitamin D, trace elements, and the interplay between molecules with pro- and antioxidant properties. Our understanding of the role of other small molecules, genes, proteins, and macronutrients is also rapidly changing. Recent work has elucidated relationships between oxidative stress, nutritional supplementation, and glucose metabolism. Thresholds have also been established to define adequate preoperative nutritional status.

Critical Issues: Further work is needed to establish standards and definitions for measuring the extent of wound healing, particularly for inflammatory bowel disease and ulcers. In addition, a mounting body of evidence has determined the need for adequate preoperative nutritional supplementation for elective surgical procedures.

Future Directions: A large portion of current work is restricted to model systems in rodents. Therefore, additional clinical and translational research is needed in this area to promote gastrointestinal wound healing in humans, particularly those suffering from critical illness, patients with enterocutaneous fistula, inflammatory bowel disease, and ulcers, and those undergoing surgical procedures.

Keywords: surgical wound healing, nutrition, trace elements, antioxidants, Vitamin D, probiotics

SCOPE AND SIGNIFICANCE

WOUND HEALING IN ONE FORM OR another is critical to numerous aspects of medicine, particularly surgery. While it may be intuitive that nutrition should facilitate wound healing, it has not until recently been apparent which pathways might be involved. This lack of knowledge has hampered patient care and resulted in increased complications and even

mortality. Furthermore, without a clear understanding of the effect of nutrition on wound healing at the molecular and cellular level, it is not possible to deliver nutrition or supplements to improve patient outcome.

TRANSLATIONAL RELEVANCE

Even though recent work has delivered new knowledge regarding the effect of macronutrients and

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micronutrients on mechanisms, at the cellular level, the bridge between this understanding and adequate clinical practice has yet to be built. Furthermore, understanding complex multisystem relationships, such as those involving oxidant and antioxidant pathways as they interact with glucose metabolism in critically ill patients, adds another level of difficulty in implementation of new nutritional supplements and standards.

CLINICAL RELEVANCE

Without an adequate understanding of nutrition and its effects on patients, particularly in the perioperative period and for critically ill patients, we risk poor outcomes and even increased mortality. While complications like surgical site infection and pneumonia may require a course of antibiotics or prolong hospital stay, those complications resulting or worsened by poor nutrition include anastomotic leak and enterocutaneous fistula, either of which can result in sepsis and death. Other clinical problems requiring an appropriate understanding of the nutritional contribution of gastrointestinal wound healing include ulcers and inflammatory bowel disease, which contribute to significant morbidity and healthcare costs.

BACKGROUND

The wound healing cascade follows a similar complex cellular and biochemical cascade in all tissues. In the gastrointestinal tract healing may involve only the mucosa as observed in inflammatory bowel disease,¹ and ulcers,² and the full thickness of the bowel as commonly observed after creation of surgical anastomoses.³ Unresolved mucosal healing can lead to full-thickness fibrosis due to continued inflammation, so rapid resolution of mucosal injury is a goal of all medical interventions. Although beyond the scope of this review, establishing common standards by which to define the extent of mucosal healing are lacking for both inflammatory bowel² and ulcer disease.⁴ As true for all instances of wound healing, in particular collagen synthesis, provision of adequate energy (to sustain synthetic processes), amino acids (as building blocks for collagen synthesis), oxygen, trace minerals and vitamins (all of which are key for optimal synthetic enzyme function) is key to successful repair.

This review will start with a discussion of the role of specific micronutrients, such as vitamin D, trace elements, and molecules with antioxidant properties. Subsequently, we will review the role of other small molecules, genes, and proteins (Fig. 1) and finally the role of macronutrients, including

both probiotics and nutritional supplementation in general, will be examined.

DISCUSSION OF FINDINGS AND RELEVANT LITERATURE

Nutritional assessment and intervention

Overall, a well-formulated nutritional strategy can improve outcomes for complex wound healing in the gastrointestinal tract; conversely, malnutrition is closely linked as an independent risk factor for complications following gastrointestinal surgery. Such surgery often require bowel anastomoses to heal successfully to prevent leakage of bowel contents, sepsis, and even death, and this process is highly dependent on the nutritional state of the patient. Malnutrition is an independent risk factor for poor surgical outcome, including death, wound complications, and prolonged hospitalization. Frequent causes of nutritional deficiency include inflammatory bowel disease, changes in metabolism due to malignancies, and systemic inflammation.⁵

Goals for nutritional optimization before surgery include adequate caloric and protein intake and provision of needed micronutrients.⁶ One additional factor to be considered is the nexus between inflammation, oxidative stress, glucose metabolism, and increased metabolic rate due to surgery.⁷ Elevations in metabolic rate can persist for months or even years after surgery.⁶ Glycemic control in the preoperative and perioperative periods can be beneficial to reduce the incidence of infectious complications, and the magnitude of inflammation, and oxidative stress. A structured preoperative nutrition plan favoring enteral nutrition over parenteral nutrition can benefit successful outcome.⁶ In the subset of patients that cannot tolerate sufficient nutrition via an enteral route, parenteral nutrition should be administered for 5–7 days preoperatively. In severely malnourished patients, preoperative parenteral nutrition can offer lower rates of noninfectious complications without an increase in infectious complications. It should be emphasized that only severely malnourished patients (Nutritional Risk Screening 2002 [NRS-2002] scores 5–6) who cannot tolerate enteral feedings demonstrate benefit with parenteral nutrition.⁶ Elective colorectal surgery should be delayed until an preoperative albumin level of 3.3–3.5 g/dL is achieved.⁸ Malnourished rats that received preoperative nutritional support had higher anastomotic tensile strength compared with controls.⁹ A recent Cochrane analysis also supports the strong influence of preoperative nutritional support in gastrointestinal surgery.¹⁰

Figure 1. Families of molecules associated with the nutritional aspects of gastrointestinal wound healing. These include amino acids, specifically arginine, ornithine, glutamine, glutamate, threonine, methionine, cysteine, serine, and proline. Also included are polyamines, which are derivatives of amino acids, short chain fatty acids (butyrate is shown), vitamins A, C, and D, long chain fatty acids like arachidonic acid, and phospholipids such as lysophosphatidic acid. To see this illustration in color, the reader is referred to the web version of this article at www.liebertpub.com/wound

The same is not true for postoperative parenteral nutrition. Patients receiving parenteral nutrition in addition to *ad libitum* oral intake following total cystectomy had a higher incidence of postoperative complications, with no significant improvement in nutritional markers.¹¹ Critically ill patients have been demonstrated to have lower infection rates, shorter length of mechanical ventilation, and reduced dependence on renal replacement therapy if they receive total parenteral nutrition on or after the eighth hospital day.¹² However, if critically ill patients cannot tolerate sufficient enteral feedings, there is data to support a mixed nutritional plan involving both enteral and parenteral supplementation.¹³ For postsurgical patients, some class C evidence exists to justify parenteral supplementation if 60% of estimated nutritional needs cannot be administered enterally after 3 days.¹⁴

Patients with enteroatmospheric fistula, an entity that is often noted after trauma or abdominal catastrophe, have complex nutritional requirements exacerbated by persistent loss of fluid, electrolytes, and protein through both the fistula and the frequently associated open abdominal wound.¹⁵ These patients require frequent assess-

ment of their nutritional status and nutritional needs. Losses of 1 g protein/500 mL of fistula output and 29 g protein/L of wound exudate have been recorded. Typical nutritional needs are for 25–35 kcal/kg/day of nonprotein calories and 1.5–2.5 g/kg/day of protein¹⁵; the only situation with a more dire nutritional situation is a large full-thickness burn. However, overfeeding is also injurious as it can result in prolonged insulin resistance and respiratory insufficiency.¹⁶ Enteral nutrition is the preferred route of nutritional support in these patients, with reduced length of intensive care unit stay and reduced incidence of infections. The only contraindications include intestinal discontinuity (usually a temporary phenomenon) and short bowel syndrome.¹⁶ However, the means of enteral nutrition must frequently be individualized for the patient based on the location of the fistula and may require supplementation with parenteral nutrition as well.¹⁵ Supplementation of trace elements and vitamins, such as zinc and vitamin C, is also required at supranormal levels due to fluid and wound losses.¹⁶ Even patients who are initially dependent on parenteral nutrition may eventually progress to reduced dependence on intravenous nutrition and in some cases can become completely

self-sufficient with enteral supplementation through the gradual process of intestinal adaptation. Special enteral nutritional formulations, incorporating partially or completely broken down components to facilitate absorption, may be required in patients with short bowel syndrome.¹⁶ The management of this challenging patient population is complex and frequently requires a multidisciplinary team with experts in nutrition, surgical care, and wound care all involved in the patient's plan of care.

Finally, in the case of inflammatory bowel disease, there is evidence linking nutritional supplementation strategies in improvement in symptomatology, implying improved healing in the gastrointestinal tract. Omega-3 polyunsaturated fatty acids (PUFA), after being metabolized to anti-inflammatory prostaglandins and leukotrienes, suppress RNA for interleukin-1 (IL-1). IL-1 synthesis and tumor necrosis factor alpha (TNF- α) synthesis are both inhibited by supplementation with omega-3 long chain fatty acids. Omega-3 PUFA have also been demonstrated to inhibit the synthesis of proinflammatory cytokines in a mouse model, thus inhibiting the recruitment of myeloid cells and improving both wound healing and the barrier function of the gastrointestinal mucosa. Furthermore, PUFAs also suppress the proliferation of CD4⁺ T-cells and Th1 helper cells.¹⁷ Increased intake of dietary fiber has also been shown to decrease levels of TNF- α and increase production of short chain fatty acids, including butyrate, whose effects have been previously discussed.¹⁷ On a broader level, determining overall nutritional strategy also has an effect on gastrointestinal tract wound healing in Crohn's disease. Exclusive enteral nutrition has been shown to be beneficial in pediatric patients with Crohn's disease,¹⁸ and in some cases yields dramatic improvements in the levels of proinflammatory mediators such as IL-1, IL-2, IL-8, and interferon- γ . Elemental and polymeric diets have also been shown to have anti-inflammatory effects *in vitro*, although not in a live model. Enteral nutrition also improved the levels of insulin-like growth factor (IGF)-1 and IGF-binding protein, which were correlated to improved clinical outcome.¹⁷

Vitamin D

Vitamin D plays a significant role in the innate immune response to bacteria, fungi, and viruses through the creation of antimicrobial peptides such as defensin hBD-2 and cathelicidin. Furthermore, through the interaction between pathogen-associated molecular patterns and Toll-like receptors (TLRs) 2/1 and 4, the activity of the

1- α -hydroxylase enzyme is increased, resulting in the production of the physiologically active twice-hydroxylated form of vitamin D. In turn, human α -defensins HNP 1–4 and HD 5–6, β -defensins hBD 1–4, and cathelicidin LL-37 are all upregulated. These proteins preserve the integrity of the barriers in the gastrointestinal tract, control the communal bacteria that usually reside in the gastrointestinal tract, and help to resist invasion by other pathogens.¹⁹ The physiologically active hormone also upregulates occludin, connexin 43, and E-cadherin activity, which is required for tight junctions, gap junctions, and adherens junctions in the intestinal mucosa, respectively.¹⁹ Vitamin D may also play a role in reducing fibrosis in Crohn's disease, as an analog reduces profibrotic responses in colonic myofibroblasts.²⁰

Antioxidants

There is a relationship between tissue injury, inflammation, and oxidative stress that can be observed in the pathogenesis or healing of injured tissue in the gastrointestinal tract (Fig. 2). Specific instances include gastrointestinal anastomotic healing, peptic ulcer disease, and inflammatory bowel disease.⁷

Caffeic acid phenethyl ester (CAPE) is a natural compound derived from the bark of conifer trees with anti-inflammatory and antioxidant effects. In adult rats with induced peritonitis via cecal ligation and puncture with subsequent left colonic anastomosis, anastomotic specimens in the CAPE-treated group were found to have a higher anastomotic bursting pressure on postoperative day 7. CAPE treatment led to higher levels of reduced glutathione and malondialdehyde (MDA), increased superoxide dismutase activity, and lower levels of myeloperoxidase (MPO) activity in the colonic wall, indicating a relationship between antioxidant activity and improved gastrointestinal wound healing.²¹

Ulcer healing is modulated by prostaglandins. Topical application of prostaglandins enhances healing of ulcers caused by acids, bile, or chemical irritants. Topical administration of prostaglandins after the application of mild irritants such as 20% ethanol, concentrated salt solution, or taurocholate protects against the later application of much more concentrated or toxic doses of the same substance even after just a few minutes. This "adaptive cytoprotection" is mediated by nitric oxide (NO) via expression of endogenous prostaglandins.²² NO exerts a beneficial effect on healing by improving blood flow to the injured area. NO appears to be the final common pathway for healing induced by other

Figure 2. Interplay of pro- and antioxidant moieties in the activation of wound healing pathways. Antioxidant molecules are involved in activation of numerous growth factors, including epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), the b isoform of fibroblast growth factor (b-FGF), and transforming growth factor alpha (TGF- α). These act as ligands that activate transmembrane G-protein-coupled receptors (GPCR), that in turn result in nitric oxide (NO) secretion. NO activates downstream pathways that increase blood flow to injured areas of the gastrointestinal tract and also alters gene expression as a diffusible transmembrane signaling molecule. Pro-oxidant molecules such as high-mobility group box 1 (HMGB1) result in activation of subsets of the Toll-like receptor (TLR) family and the receptor for advanced glycation end products (RAGE). TLR and RAGE result in increases in the levels of myeloperoxidase (MPO), interleukin-1 (IL-1) and tumor necrosis factor alpha (TNF- α), thus inhibiting downstream pathways that facilitate wound healing in the gastrointestinal tract. To see this illustration in color, the reader is referred to the web version of this article at www.liebertpub.com/wound

factors such as epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), transforming growth factor- β (TGF- α), the b isoform of fibroblast growth factor (b-FGF), and platelet-derived growth factor (PDGF). Of note, formulations involving topical treatment with EGF have also been shown to ameliorate gastric ulcers in rabbit and pig models.²³ The gastroprotective effects of ghrelin, leptin, and other gastrointestinal (GI) tract hormones may also be attributable to NO, as inhibition of NO reverses the effect. COX inhibitors such as aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) can be structurally modified to include a nitric oxide moiety, thus ameliorating their injurious effect to the gastric mucosa. Proton pump inhibitors both suppress acid secretion and exert an antioxidant effect that reduced MDA levels even if ulcerogenic indomethacin is administered concomitantly.²⁴

A pentadecapeptide termed body protection compound (BPC) 157 has been studied in a rat model of esophagocutaneous fistula in which heal-

ing deficits may be related to insufficient levels of NO—and therefore decreased blood flow. Control animals have a 70% mortality after 4 days, but there was improved healing and survival in the group given BPC 157. Nitro-L-arginine methyl ester (L-NAME), a nitric oxide synthase (NOS) inhibitor, has been demonstrated to worsen ulcer formation. However, these effects were counteracted by both L-arginine and BPC 157.²⁵

Asymmetric dimethylarginine (ADMA) is an arginine derivative whose levels are increased by oxidative stress. ADMA acts as a competitive inhibitor for the NOS enzyme, thus reducing the bioavailability of NO and also contributing directly to oxidative stress.²² ADMA levels are significantly increased in specimens of gastric mucosa infected with *Helicobacter pylori* and thus ADMA could play a role in the pathogenesis of *H. pylori*-induced mucosal damage as well. ADMA levels were increased in gastric specimens exposed to water immersion and restraint stress (WRS) or ischemia and reperfusion injury, but this increase was re-

versed by the administration of L-arginine, a substrate for NOS, and superoxide dismutase, a free radical scavenger. ADMA administration has been shown to increase the number of lesions caused during WRS and also reduced the levels of gastric blood flow.²²

The nexus of inflammation, oxidative stress, glucose metabolism, and wound healing is best exemplified by the role of high-mobility group box 1 (HMGB1), a nuclear protein that acts to stabilize nucleosomes. TLR2 and TLR4 are activated by extracellular administration of HMGB1, as is the receptor for advanced glycation end products (RAGE). Healing of acetic acid-induced ulcers in mice was inhibited by HMGB1 administration and oxidative stress was elevated through increased MPO and TNF- α expression. Further experiments demonstrated that the effect of HMGB1 was dependent on TLR4 and RAGE, but not TLR2.²⁶

Although it is too early to determine whether these preclinical and basic studies in animals can lead to clinically active compounds to assist wound healing, the data available does seem to indicate a relationship between the oxidation cascade and resulting tissue injury in the context of wound healing in the GI tract.

Trace elements

Trace elements, including zinc, magnesium, and copper, affect motogenesis, the attraction of specific cell types to the critical binding sites in proteins or enzymes, facilitating their activity. Trefoil protein 1 (TFF1) activity, a protein involved in restoration of the epithelium after injury, is upregulated five-fold in copper-deficient rats. The copper ion also facilitates dimerization of the TFF1 protein, and this was blocked by ethylenediaminetetraacetic acid (EDTA), a metal chelating agent.²⁷

A zinc-magnesium alloy was noted to have lower numbers of infiltrating lymphocytes and neutrophils via histological analysis when compared with a control titanium-aluminum alloy. It was noted that the zinc-magnesium alloy implanted into the gastrointestinal tract degraded over a period of several weeks whereas the titanium-aluminum alloy did not. Furthermore, immunohistochemical staining indicated decreased levels of TNF- α and increased levels of TGF- β , VEGF, and b-FGF expression. Thus, it was postulated that the zinc-magnesium alloy, a putative material with which to make staples for gastrointestinal tract anastomoses, resulted in decreased levels of inflammatory mediators and therefore reduced levels of cellular infiltration.²⁸

Zinc-containing proteins such as Kruppel-like factor 5 (KLF-5) are involved in multiple cell pro-

liferative processes, including in healing after dextran sodium sulfate (DSS)-induced murine colitis. KLF-5 is upregulated in specimens treated with DSS and is dependent on NF- κ B activation with resulting involvement of the mitogen-activated protein (MAP) kinase pathway. KLF-5 knockout mice have deficiencies in healing after DSS administration.²⁹

Zinc carnosine (ZnC), commonly sold over the counter as a health food supplement, contains a zinc ion and a carnosine moiety, comprising a dipeptide of β -alanine and L-histidine, in a 1:1 ratio. Carnosine may provide benefit by activating antioxidant pathways. ZnC reverses increased gut permeability associated with NSAID administration in healthy volunteers. It also promotes cell proliferation and cell migration *in vitro* in a dose-dependent fashion. Finally, ZnC administration reduces ulcer scores and the macroscopic area of damaged cells in a rat model of peptic ulcer disease induced by administration of indomethacin.³⁰ The addition of vitamin E to ZnC ameliorates peptic ulcer in a canine model.³¹ Although there is not clear evidence in human trials for supplementation of trace metals, presumably their effect is the same set of proteins—VEGF, b-FGF, and TGF- β —associated with other healing modalities.

Other small molecules

Administration of low molecular weight heparin decreases the strength of bowel anastomoses. In particular, low molecular weight heparin and its unfractionated counterparts reduce expression of b-FGF, VEGF, and PDGF via direct binding, thus decreasing angiogenesis, which is a crucial first step for successful wound healing. Furthermore, heparin blocks collagen production in fibroblasts, and reduces fibroblasts viability *in vitro* by inhibiting incorporation of thymidine into DNA.³² However, this did not appear to affect parameters of colon anastomotic healing in a rat model.

Administration of the short fatty acid butyrate via an enema increases the strength of left colonic anastomoses. Known as a nutrient for colonocytes, butyrate also may reduce the rate of collagen breakdown through a decrease in the levels of matrix metalloproteinases (MMPs).³³ Butyrate also enhances the proliferation of enterocytes and colonocytes, although it is unclear whether the mechanism only involves the role of butyrate as an energy source or other neurohormonal mechanisms.³⁴ Of note, one of the mechanisms by which infliximab, an anti-TNF- α monoclonal antibody, may reduce inflammation in human inflammatory bowel disease is through reduction in MMP levels.³⁵

The same molecular mechanisms apply in the case of wound healing in ulcer disease. The action of sucralfate goes beyond simply supplementing the mucosal barrier of the gastric epithelium and includes stabilizing acid and base (a and b)-FGF and preventing their degradation. This therefore allows continued angiogenic activity, resulting in improved healing. Furthermore, sucralfate also results in an increase in the expression of TGF- α and binds EGF in a pH-dependent fashion, also facilitating wound healing. EGF and PDGF receptors are also upregulated as a result of sucralfate's actions. Sucralfate also acts through the cyclooxygenase pathway to increase levels of prostaglandin E2, scavenges free radicals, and inhibits apoptosis by preventing the activation of caspase-3.³⁶

Finally, in the case of colitis, anagliptin serves as an inhibitor for dipeptidyl peptidase-4 (DPP-4), which is in turn an inhibitor of glucagon-like peptides 1 and 2 (GLP-1 and -2), which serves as a gastrointestinal growth factor. GLP-2 is secreted by gut endocrine cells after nutrient administration and stimulates the proliferation of crypt cells and inhibiting apoptosis. Anagliptin demonstrated inhibition of DPP-4 activity and also reduced the disease activity index in a DSS-induced rat model of colitis.³⁷ It is worth noting that this is a relatively unique mechanism not involving VEGF or angiogenesis.

Probiotics

Probiotics are defined by international consensus as live microorganisms that can provide a health benefit to their host if given in an appropriate amount.³⁸ Such microorganisms do not have to adhere to the intestinal epithelium to be considered probiotics and do not have to be of human origin. Probiotics are not robustly regulated in the United States and the purity or effectiveness of any particular formulation cannot be independently verified.³⁸

Probiotics have been studied as a means to accelerate or improve healing of the mucosa after formation of a gastric ulcer. It is thought that probiotics upregulate growth factors, such as ornithine decarboxylase (ODC), B-cell lymphoma 2 (Bcl-2), VEGF, and epidermal growth factor receptor (EGF-R) and inhibit apoptosis.³⁹

An inoculum of either 1×10^8 or 1×10^9 viable colony forming units of *Lactobacillus rhamnosus* GG was administered twice-daily via gavage feedings for 3 days. Acetic acid-induced gastric kissing ulcers resulted in a decreased incidence of terminal deoxynucleotidyl transferase deoxyuridine triphosphate nick end labeling (TUNEL)-positive

cells, indicating a reduced level of apoptosis, while simultaneously showing $\sim 41\%$ more angiogenesis than the control specimens. *Lactobacillus*-inoculated specimens had higher expression of Bcl-2 and ODC. *Lacto-bacillus*-inoculated specimens also had higher levels of VEGF expression, correlating with the increased neovascularization seen histologically. Increased EGF-R phosphorylation was also seen, correlating with decreased apoptosis and increased levels of angiogenesis.³⁹

A mixture of different bacterial species including four types of *Lactobacillus* (*acidophilus*, *bulgaricus*, *casei*, and *plantarum*), three types of *Bifidobacteria* (*breve*, *infantis*, and *longum*), and a single *Streptococcus* species were applied also to acetic acid-induced gastric ulcers. Healing occurred in 30% of the low-inoculum samples (6×10^9 colony-forming units) at day 7 and 57% by day 14. For high-dose samples (1.2×10^{10} colony-forming units), healing occurred in 57% by day 7 and 84% by day 14. The differences were statistically significant for high-dose samples at day 7 and 14, and for low-dose samples at day 14. Expression of VEGF, EGF, and TGF- β were both increased in the treatment groups in a dose-dependent fashion. Furthermore, a VEGF-neutralizing antibody reversed the accelerated wound healing seen in the treatment samples.⁴⁰

Taking the two reports together, there is certainly a reasonable level of evidence in the pre-clinical literature that angiogenesis may be a crucial component of wound healing after gastric ulceration. Likewise, there is some evidence that the use of probiotics might accelerate this process, but the mechanism by which the administration of probiotics increases VEGF expression is unclear and requires further study.

SUMMARY

We have provided an update of the role of nutrients on mucosal and full-thickness healing in the gastrointestinal tract. Clearly, maintenance of host nutritional state or restoration of adequate nutritional indices is a priority and has a major influence on healing outcomes. Much experimental data on individual nutrients has been generated, but lack as yet firm application in the clinical arena. Nutrients can and will influence healing in the gastrointestinal tract, but further work is needed.

AUTHOR DISCLOSURE AND GHOSTWRITING

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TAKE-HOME MESSAGES

- Understanding the role of nutrition in gastrointestinal wound healing is of greatest importance for disease processes as postsurgical healing, ulcer disease, inflammatory bowel disease, and enterocutaneous fistula.
- A comprehensive strategy is necessary to approach preoperative and postoperative nutrition for the surgical patient, as malnutrition is associated with increased morbidity and mortality.
- Primary emphasis should be on providing enteral nutrition, with the exception of preoperative nutrition in severely malnourished surgical patients.
- There is an evolving understanding of the relationship between nutrition, glucose metabolism, inflammation, and oxidative stress.
- Vitamin D has a significant role in preserving defenses against bacteria, fungi, and viruses.
- Trace elements often serve as critical cofactors that facilitate enzymatic activity that is necessary for wound healing in the gastrointestinal tract.
- A variety of other small molecules, including low molecular weight heparins, butyrate and other short chain fatty acids, sucralfate, and anaglitin act via multiple downstream mediators to facilitate wound healing.
- Tyrosine kinase receptors, including b-FGF, TGF- β , PDGF, EGF, and VEGF, are key mediators in facilitating wound healing.

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Abbreviations and Acronyms

ADMA	= asymmetric dimethylarginine
Bcl	= B-cell lymphoma
BPC	= body protection compound
CAPE	= Caffeic acid phenethyl ester
DPP	= dipeptidyl peptidase
DSS	= dextran sodium sulfate
EGF	= epidermal growth factor
EGF-R	= epidermal growth factor receptor
FGF	= fibroblast growth factor
GI	= gastrointestinal
GLP	= glucagon-like peptide
HMGB	= high-mobility group box
IGF	= insulin-like growth factor
IL	= interleukin
KLF	= Kruppel-like factor
MDA	= malondialdehyde
MMP	= matrix metalloproteinase
MPO	= myeloperoxidase
NO	= nitric oxide
NOS	= nitric oxide synthase
NSAID	= non-steroidal anti-inflammatory drug
ODC	= ornithine decarboxylase
PDGF	= platelet-derived growth factor
PUFA	= polyunsaturated fatty acids
RAGE	= receptor for advanced glycation end products
TGF	= transforming growth factor
TLR	= Toll-like receptor
TNF- α	= tumor necrosis factor α
VEGF	= vascular endothelial growth factor
WRS	= water immersion and restraint stress
ZnC	= zinc carnosine