Nutrition and Wound Healing

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Abstract

A review of the literature reveals that unfavourable surgical outcome, including problems with wound infection and dehiscence, sepsis, and longer lengths of stay, correlates well with the determination of perioperative malnutrition as measured by a variety of indices. Increased malnutrition and more severe surgeries are individually predictive of poorer outcome. There is evidence that particular deficiencies of nutrients are likely to cause wound healing problems. Particularly important nutrients include amino acids (notably glycine, proline, and arginine) carbohydrates, fatty acids (especially linoleic and linolenic), vitamins (particularly C and A), minerals and the elements (particularly magnesium, copper, phosphorous and selenium).

The postoperative feeding of seemingly large amounts of amino acids is correlated with positive nitrogen balance and shorter hospital stays. The enteral route is preferred unless there is disturbed absorption or other complications. Total parenteral nutrition (TPN) formulations should include all of the essential nutrients, especially trace elements which were formerly overlooked.

Introduction

With surgery, as with trauma and sepsis, there is an increase in the requirement for calories, amino acids, vitamins, minerals, water and oxygen.

This paper reviews the possible relationship between certain nutrients and wound healing, evidence pointing to a connection between perioperative nutritional status and surgical outcome (including wound healing), and information concerning route of administration and prevention of deficiencies of certain nutrients.

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Nutrients Which May Affect Wound Healing

"Wound healing is a biochemical process and that nutrition itself is really a clinical biochemistry, and an obvious relationship between these two areas exists... Nutrition has to be thought of by all clinicians as the specific nutrient substrates that are being delivered to the specific cells and tissues at a given time. This is where nutrition really occurs, at the cell mem brane and in the cell, and it is only when we realize this and practice surgery with this in the proper context that we will then achieve optimal wound healing to correlate with the technical and other aspects of wound healing in which we engage as surgeons."[1] **H. Polk**

Protein and Amino Acid Balance

Surgery, trauma and sepsis introduce a protein catabolic state.[2] Wound healing is in part dependent on the ability of the body to provide adequate amounts of amino acids. Animal studies conducted by Harvey and Gibson showed that simultaneous supplementation with glycine, proline and arginine produced an increase of as much as 60-70% in nitrogen retained.[3] This effect may be reversed if glycine alone is used.[4]

Arginine, which can be converted to proline, is associated with more rapid wound healing and greater collagen synthesis in animal models and may even inhibit post-trauma weight loss.[5 6] Furthermore, arginine-deficient rats rapidly lost collagen.[5] Glycine accounts for approximately one-third of all amino acids found in most collagen alpha chains.[7] Glycine and arginine are shown to be necessary for the synthesis of creatinine and for optimal growth in experimental animals.[6] Furthermore, arginine detoxifies ammonia and detoxifies benzoic acid. Glycine may play a part in the repair of muscle fibers.[4] Arginine converts to ornithine glutamic semialdehyde and proline, leading to proline's conversion to collagen. Arginine can also be converted to lysine.[4] There are about 200 proline residues and thirty-five lysine residues in the alpha collagen strands.[7]

Hypoalbuminism has been associated with impaired healing of forearm wounds in adults.[8] It is thought that the lower plasma albumin levels often observed following injury relate to slowed synthesis and increased deposition at wound sites. (An increase in absolute catabolism of albumin is not observed.[9]) Plasma albumin is thought to act as an amino acid donor at wound sites and as a transporter of zinc, fatty acids, and sulfur-containing amino acids.[10]

Research suggests that nitrogen is more likely to be pulled from muscle tissue in surgical stress and the liver is likely to be spared.[9] Even the early stages of protein-calorie malnutrition have been correlated with impaired wound healing not unlike that of advanced malnutrition.[26] There is some evidence that slow scar formation in humans nevertheless results in normal scar tissue.[11]

Carbohydrates and Fats

Fatty acids are essential for the transport of substances across cell membranes. The optimal level of fat consumption for wound healing has not been determined but 20% or more is common in hospitals. Moderate liquid levels can reduce the potential hypoglycemic effect of high glucose feeding. A deficiency in essential fatty acids is associated with poor wound healing.[12] However, an experiment involving over 30% fat in a total parenteral formula yielded very unsatisfactory postsurgical results. It was thought that the fat inhibited the movement of leukocytes which are essential for the prevention of sepsis and stimulation of scar tissue formation.[13] Both carbohydrates and fats are important in that they provide calories, have a protein sparing effect and provide energy. Generally, it is necessary to use combinations of energy sources and proteins/amino acids in order to preserve or augment nitrogen balance. If less than caloric need of carbo-hydrate/lipid is given, it is also difficult to achieve positive nitrogen balance.[14] Usually carbohydrates provide the bulk of calories for perioperative patients regardless of route.

Water

Subcutaneous tissue is highly influenced by vasoconstriction and can be poorly hydrated while the brain, liver, heart and kidney are well perfused. Studies show that dehydration is associated with low tissue pO_2 and increased catabolism.[15] Such patients are considered to be more susceptible to infection. One might postulate that supplies of other essential nutrients to wounds would be impaired as well by dehydration. When dialysis and heavy loads of water are used, the purity of water (i.e. low levels of aluminum and lead) is essential.

Oxygen

Subcutaneous hypoxia can be found in 33 to 80% of postoperative patients.[15] Most cases can be returned to normal tissue oxygen levels through vigorous hydration efforts and administration of a higher % of oxygen. Medicine needs an easy, accurate way to measure tissue oxygen. Until this exists, aggressive measures to ensure hydration are essential to safeguard against hypoxia.[15]

A state of slight hyperoxia (obtainable usually with either normobaric or hyperbaric oxygen administration) can increase leukocyte bacterial-killing activity. This effect will be additive when done in conjunction with antibiotics. Hyperbaric oxygen treatment raising arterial pO_2 to over 1,000 - 2,000 mm Hg for 1 hour per day may be adequate to stimulate effective leukocyte bacterial killing. (Surgical manipulation of blood supply can also be used to create hyperoxia.[15]) Davis cites studies that showed that ischemia lowers local immunity and that, in one study, infections were found only in subjects with tissue pO_2 below 30 to 40 torr. Low pO_2 can result in poorly hydroxylated collagen which has less thermal stability.[7]

Vitamins, Minerals and Wound Healing

Vitamins are essential for wound healing. Gerber found increased tensile strength in the wounds of rats fed supplemental retinylacetate, beta-carotene, or retinoic acid (all forms are precursors of vitamin A) with measurably stronger scar tissue.[16]

Vitamin A has also been shown to have a beneficial effect on the healing of colonic anastomoses.[17] Additionally, the increased risk of anastomotic breakdown, leakages, and spontaneous perforations seen both early and late after radiotherapy may be ameliorated by vitamin A therapy with significant mitigation of the decreased bursting strength and hydroxyproline content of the tissues which is seen after radiotherapy.[18 19 20]

Of interest, an actual deficiency of vitamin A may not be required for impaired wound healing. Niu reported increased hydroxyproline content at the site of arterial anastomoses and increased bursting strength at distant sites in rats supplemented with moderate levels of vitamin A over that seen in controls who were themselves on diets several times the National Research Council's RDA.[20]

Topical vitamin A appears also to have its uses; it may reverse the inhibitory effect of steroids on healing wounds perhaps by affecting leukocyte numbers involved in the inflammatory and wound healing process.[19]

Vitamin A can restore epithelialization in the presence of glucocorticoids which would otherwise suppress macrophage activity and hence wound healing. It cannot, however, overcome the suppressive effect of glucocorticoids on wound contraction.[21]

Vitamin E is a free-radical scavenger which preserves macrophages and poly-nuclear leukocytes from the lipid peroxides that they make.[22] However, if a vitamin E deficiency exists, there may be some impairment of wound healing.[13]

Vitamin C is an essential co-factor in the formation of collagen.[17] One of the symptoms of scurvy is the weakening and dehiscence of old wounds.[25] Decreased tensile strength was found in the excised wounds of skin and facia lata in subjects deficient in vitamin C.[13] In a double blind study, vitamin C 500 mg with meals and at bedtime produced a decrease of 43% versus 84% in patients with decubitus ulcers.[26]

The authors feel one striking anecdote concerning vitamin C and wound healing deserves telling. In a panel discussion by leading surgeons, one participant spoke of treating a cancer patient's infected maxillary wound in the pre-antibiotic era with vitamin C. He stated, "I had read that in an individual who has infection, vitamin C is depleted, and although this man had no evidence of scurvy, I thought it might be a case of sub-clinical scurvy, so I gave him what I thought at that time was an enormous quantity of vitamin C, 1000 mg a day, and immediately the wound began to heal and the infection was controlled, and he got well, so this made an impression upon me."[15]

Thiamine deficiency interferes with collagen synthesis; granulation tissue was one-fifth normal in thiamine-deficient rats.[24] Pantothenic acid may accelerate the wound healing process; when 20 mg/kg/ day was given to rabbits, aponeurotic strength and number of fibroblasts increased.[25] Riboflavin is identified as an important mediator of wound healing.[9]

Zinc is a mineral which is important for the action of collagenase, the enzyme which breaks down collagen.[4] Since 25% or more of the collagen formed in the first week of wound healing is normally broken down,[27] the importance of zinc can be inferred for the remodeling and strengthening of surgical wounds. One author suggests, however, that significant depletion of zinc stores must exist before it is an issue. Zinc metalloenzymes include DNA polymerase, superoxide dismutase and reverse transcriptase. Zinc is depleted by stress and suppressed by the influence of ACTH and anabolic steroids which are elevated in the post-surgical patient.[22] Achieving the right balance is the issue. Pories and others found in 1967 that zinc sulfate given orally accelerated wound healing in one patient. Furthermore, Pories and colleagues found that zinc was important to the rapid reduction of wound cavity in excision of pilonidal cysts.[23]

Zinc will reduce copper stores if used in excess. Copper is also essential to proper wound healing as it is a co-factor for the action of lysyl amine oxidase (LAO) in the aldehyde reactions which generate strong covalent bonds in collagen.[7 28] Selenium is also considered important for wound healing. Manganese is necessary for the glycosylation of hydroxyproline residues in the formation of collagen.[7]

Effects of Nutritional Status on Surgical Outcome and Wound Healing

It would be difficult to prove without a doubt that strong wounds are formed by providing adequate nutrition to patients or that they form faster. Most wound research involving tensile or bursting strength or even speed of wound healing has been done with animals and there are problems in assuming rat or guinea pig wound healing physiology sufficiently parallels that of humans.

Most of the evidence that nutritional status plays an important role in wound healing in humans is more indirect. There are many studies correlating nutritional status (pre- and/or post-operative) to surgical outcome (e.g., number of complications such as ruptured anastomoses, dehiscence, infection, sepsis and length of stay).

Evaluating Patients At Risk

The prevalence of some degree of malnutrition (protein-calorie and/or vitamin deficiency) is high among medical and/or surgical patients. Buzby reviewed three studies and concluded that about 50% had some degree of protein-calorie malnutrition, regardless of medical specialty or socioeconomic background.[29] A table summarizing such epidemiologic surveys shows 30% to be the lowest rate among major surgery patients with 45-50% the most common rate of protein-calorie malnutrition. Hypovitaminemia was found in 50% of medical and surgical patients at one New Jersey hospital.[30] Fortunately, serious malnutrition is found less frequently. Severity of complications correlate with the degree of malnutrition and with the seriousness of surgery.[30] The surgeon must take into account the type and extent of surgery to be performed in evaluating risk.

It is estimated that surgical patients lose 4-8% of their body weight for minor surgery and 15-25% for major surgery.[31] Experts advocate taking a very careful nutritional history for all surgical patients, covering: weight loss and its time frame and possible causes; dietary habits; surgical history; unorthodox diets, use of medications, drugs or alcohol, food intolerance, functional capacity of the gastrointestinal tract; the presence of fever, tachycardia; catabolism; irritable bowel syndrome, or short bowel syndrome. The physical examination can provide useful information on anthropometric measurements, edema, muscle, wasting and the various signs of deficiencies. Malnutrition is often accompanied by CNS depression, lowered ventilatory drive and blood pressure, bradycardia, achlorhydria, irritability, apathy, and inability to concentrate.[32] Growth hormone is depressed but thyrotrophic and adrenotrophic are not. Objective criteria are used to determine degree of malnutrition though few utilize all of these measurements: secretory proteins (albumin, transferrin, prealbumin, retinol binding protein), skeletal protein (24-hour urinary creatinine divided by height), muscle degradation (urinary 3-methylhistidine), and various anthropometric determinations (weight-for-height, triceps skinfold, mid-arm circumference).[32] Immunologic indications (skin test reactivity, complement levels and total leukocyte counts), metabolic profiles, and tests of critical organ function have all been associated with nutritional status.[33]

Correlating Nutritional Status With Surgical Outcome

To review some of the early research, Dr. Radin and others at the University of Pennsylvania produced a hypoproteinemic state in dogs during the 1930's and observed retarded gastric emptying times in animals which had gastroenterostomies. Moreover, there were several wound breakages and he attributed this to delayed fibroplasia.[13] With human subjects, as early as 1936, Studley showed an association between poor nutritional and surgical outcome, describing how surgical risk increased eight-fold (33.3 vs 3.5%) in patients with benign chronic peptic ulcer disease who had lost more than 20% of their body weight as compared with those who had no loss.[34] Controversy arose, however, over the implications of this study, i.e., is this association causal and, consequently, is perioperative nutritional supplementation warranted?[29]

Several other studies have answered in the affirmative. Muller randomized 125 surgical patients for ten days to either a typical hospital diet or total parenteral nutrition (TPN) preoperatively. Those on TPN had increased serum total protein, transferrin, albumin, and immunoglobulins as well as skin test responsiveness. Postoperative morbidity (intra-abdominal abscess, peritonitis, anastomotic leakage, ileus) was decreased albeit not significantly; however, the number of patients requiring artificial respiration was increased, again not significantly.[35]

Mughal (1987) studied thirty-two patients with clinical and laboratory evidence of malnutrition (serum albumin < 3.5 and recent weight loss > 10% plus any two of the following at or below the tenth percentile: weight for height, midarm circumference, triceps skinfold. They were found to have greater postoperative morbidity and mortality when compared to their well-nourished counterparts. In addition, if complications did occur, it took the malnourished patients twice as long to achieve satisfactory oral intake.[36]

The Cardiff study was able to demonstrate a significant decrease in the incidence of wound infections in those given parenteral nutritional support (40% vs 83%).[37] Gill and Mequid showed a correlation between complications (poor wound healing, increased fatality rates, longer hospitalization) and the severity of malnutrition in major surgery.[38] [39] Hospital duration was decreased as much as four to six days in two out of three studies of colorectal surgery.[40 41 42]

Dudrick said in a panel discussion that he and colleagues from The University of Texas Medical School (Houston) assessed ninety-six patients who were to have elective hip surgery. Twenty percent were found to be nutritionally deficient, especially in protein status, when evaluated by fourteen indices. Protocol called for surgery to be done as planned. One year later 18% had significant complications (including infections and wobbling prostheses) and all of these patients had been judged malnourished at the time of surgery. Now they provide all such patients with one to three weeks of a preoperative repletional program (including occasional tube feeding) until normal nutritional status is regained.[13]

Dempsey and Mullen surveyed eighty studies dealing with nutritional status and surgical outcome. They point out that most (forty-five studies) had insufficient data to determine usefulness in terms of sensitivity, specificity and efficiency. The percentage of patients with poor nutritional ratings who have poor outcomes ranged from 1% to 100% with a mean of 65%. The positive predictive value (which is the percentage of positive tests which are true indicators for outcome) ranged from 1% to 83% with a mean of 37%. Finally, the efficiency of nutritional predictors (or the ability of nutritional ratings to predict either a good or poor outcome) ranged from 27% to 94% with a mean of 68%. The conclusion of the paper is that more rigorous research methodology is needed to evaluate the efficacy of nutritional programs in improving surgical outcome.[33]

A review of the use of nutritional indicators and concluded that predicting survival is possible 80% of the time and death, 40% of the time. Use of serial measurements (made every 10 to 14 days) allows one to predict death accurately in 78% of all cases.[29 43]

A set of simple predictive criteria used with elective surgery and other patients at M.D. Anderson Hospital and Hermann Hospital for several years is as follows: the patient is tested for three criteria — a low serum albumin (less than 3.4 g per dl), a low total lymphocyte count, and recent inadvertent weight loss or more than 10% body weight. The presence of one indicator corresponds with mild malnutrition, and rare wound disruption; two indicators correspond with moderate malnutrition and a 4-6% rate of wound disruption; three indicators are present in moderately severe to severe malnutrition and are associated with a 14% wound disruption rate. A patient who has lost 30% of their well weight in 30 to 60 days has a 30-50% chance of wound dehiscence. Tissue edema is expected in patients with serum protein below 5.5 g percent.[13]

The superiority of any one plasma protein or formula as a predictor of surgical outcome is difficult to establish. Pomp and colleagues have summarized the strengths and weaknesses of various nutritional assessment tools.[44 50] Significant underweight is an obvious and definite health risk. Changes in transferrin correlated significantly with changes in nitrogen balance ($p = .02$) but prealbumin did not in a study by Fletcher.[45] Transferrin may reduce the supply of iron to invasive organisms.[10]

Hill made a comparison of various studies and concluded that transferrin, prealbumin and the "Leeds Formula" yielded the most significant predictors. Changes in albumin are not rapid enough due to a long half-life; therefore, it is not the best protein for tracking patient progress. (It is useful for predictive outcome at the outset.) Simple determination of weight loss was quite specific for poor surgical outcome as were the Philadelphia and Boston formulas. The surgeon's assessment was 86% accurate for predicting good outcome in the presence of malnutrition but only 27% accurate for predicting a poor surgical outcome (positive predictive value).[10]

Buzby reports that patients having serum albumin levels of 2.6 g per dl or less have a less than 5% chance of survival. (Death is usually by sepsis.) The 50% chance occurs at 3.2 g per dl.[29] A rise in serum prealbumin taken weekly has been shown by Church and others to be predictive of positive nitrogen balance with a sensitivity of 88%, specificity of 70%, positive predictive value of 93% and negative predictive value of 56%. In cases of death, dropping nitrogen balance was the best indicator. Of all the plasma proteins, prealbumin was the best indicator of poor outcome.[46] However, some consider it to reflect dietary intake more than nutritional status.[44]

Warnold found that malnourished non-cancer surgery patients (having two or more abnormal values for % weight loss, body weight relative to reference weight, mid-arm muscle circumference or serum albumin) had an average length of stay of twenty-nine days versus fourteen days for normally nourished surgical patients. The malnourished group had a 31% rate of serious complications while the normals had 9% ($p < .05$).[47]

Patients showing negative response to a set of recall antigens in one study were later to have five times the normal rate of infection and mortality. Therefore when anergy is detected, physicians should assess nutritional risk carefully.[48] Many alterations in host immunity have been noted with malnutrition including decreased intracellular bacterial killing, decreased C3 (which can in turn decrease opsonic function if the level falls to 30%) and fewer lymphocytes.[48]

Several formulas may be necessary to address all types of surgery.[10] More research is needed to confirm that the observed correlations are strictly nutritional. It is evident that nutritional status has considerable effect on surgical outcome which includes wound healing. Assumptions must be questioned. For example, there needs to be a way to determine in what way feeding will improve the surgical results or if the impact of the disease is mostly responsible for the condition.[49] Determination of the optimal nutritional prognosticators of surgical outcome would help determine more exactly how to do perioperative nutrition.

Protein-calorie malnutrition can occur in surgical and chronically ill patients. Predisposing factors are many, including anorexia, malabsorption due to various gastrointestinal disorders, hypermetabolism secondary to surgery, fever, infection, inflammation, trauma, and abnormal nutrient losses, e.g., after extensive burns.[10]

Perioperative Nutrition

Some considerations in providing perioperative nutrition are covered in this section. It is beyond the scope of this paper to fully describe the benefits and risks of enteral vs. parenteral feeding, the types of feeding arrangements and possible formulas.

Method of Feeding

Briefly, it should be the principle of health care professionals to use the oral route when possible, followed by nasogastric tube, possibly jejunostomy or gastrostomy (for long-term use), then IV feeding.[10] Some feel a combination of enteral and peripheral parenteral nutrition (PPN) is less invasive than central parenteral nutrition (CPN).[32] However, CPN is the route of choice in severe malnutrition.

Enteral Feeding

Enteral feeding has the advantage of avoiding the accumulation of excess water,[50] encouraging crypt cell turnover and inhibiting villous atrophy in the gut. The stimulation of hormonal secretion may also have beneficial systemic effects. It is especially recommended in protein-calorie malnutrition with severe sysphasia, inadequate oral intake for the five successive days, massive small bowel resection (using TPN as well), and with low output enter-ocutaneous fistulas.[51]

Problems associated with enteral feeding include poor tolerance in very ill patients, diarrhea, and gastrointestinal intolerance, often due to bolus feedings.[51] Even depleted, stressed patients used only between 40 and 50 kcal/kg/day, the highest requirement going to the normally nourished, stressed patient. These patients have normal metabolic rates which have become somewhat catabolic.[10 50] A careful calculation of calorie requirement can be made using a formula provided by Horowitz.[31] Protein needs perioperatively will run from 250 mg nitrogen/kg/day for depleted, unstressed patients to 400 mg nitrogen/ kg/day for stressed patients.[10] A 70 kg man who has had uncomplicated surgery may need 70 g/day of protein and a 55 kg woman, 57 g protein.[31]

Moss (1984) describes eighteen post-cholecystectomy patients who were given full enteral nutrition with amino acids immediately postoperatively. Ten of these were given an elemental diet providing 132 g amino acids/day, eight received 66 g amino acids/day, and controls were fed with a standard hypocaloric solution. In the unfed controls, decreased branched-chain amino acids (BCAAs) were observed; these increased after three or four days and normal levels were finally restored after five to ten days. Patients receiving the higher amount of protein maintained their basal levels immediately postoperatively, then had increased levels. Intermediate amino acid feedings (66 g) had lower BCAAs for twenty-four hours then rapidly returned to normal. Moss correlates this positive protein balance and increased serum amino acid levels with enhanced wound healing, resistance to sepsis, and shortened hospital duration.[52] Other studies have confirmed the positive nitrogen balance and reduced hospital duration, but failed to show any decrease in postoperative complications.[53 55]

Parenteral Nutrition

Direct delivery of calories and nutrients to the bloodstream was first done in 1656 by Sir Christopher Wren who infused ale and wine into the veins of dogs. Various improvements over the next 300 years ensued, but it wasn't until 1967 when Dudrick and associates first developed the use of central venous lines that long-term survival on parenteral fluids was feasible.[56 57] Now, 5400 mOsm of nutritionally complete, fat-free solution can be provided, supply 3600 kcal/day and far outdistancing the previous limits of 1800 mOsm and 1000 kcal possible by the peripheral venous route.

Total parental nutrition (TPN) is indicated in patients who cannot absorb through the gastro-intestinal tract, have severe diarrhea, disease of small bowel, major surgery, enterocutaneous fistulas and extremely catabolic states, to name a few indications.[58]

Minor surgery patients are generally considered to need less aggressive nutritional support (e.g. no parenteral nutrition unless severely malnourished). Within seven days of surgery they should be ingesting a maintenance diet orally.[31] Elective colectomy patients, however, were studied for post-operative eating patterns and were shown to have an average 1,155 kcal of calorie deficity daily in the first fourteen days post surgery.[59] Patients with major surgery or injury usually need two to three times the RDA postoperatively to avoid significant weight loss. This is a fascinating example of stress producing a need for mega-nutrition. If patients have protein-calorie malnutrition, they need aggressive preoperative therapy as well.[31]

Glucose and lipid, though both partially protein sparing, are insufficient to maintain a positive nitrogen balance in the absence of exogenous amino acids.[60] However, use of dextrose-free amino acid IV solution has shown no clear benefit.[43] A full range of nutrients including carbohydrates, lipids and protein has been shown to be more effective.[61]

A fairly standard IV feeding formula today may consist of two solutions, one of amino acids, dextrose, electrolytes, vitamins, and trace elements, and another, lipid emulsion, are used in total parenteral nutrition (TPN); they are infused simultaneously. The standard first solution contains 25% dextrose and 5% amino acids in equal volumes.[23] 115-120 mmol sodium, 80-100 mmol potassium, 10 mmol calcium, 12-15 mmol magnesium, and 12-20 mmol phosphorus are routinely added. Vitamins and trace elements are introduced as required. In the average adult, 1.5-2 L/day of IV solution are given. 1.0 to 1.5 liters of lipid are infused concurrently. These two solutions provide 100 grams of amino acids, 1250-1700 kcal glucose and 1100-1650 kcal lipid for a total of 2350-3350 kcal/day.[62 63]

There are many commercially available formulas allowing for accommodation of requirements imposed by specific diseases, and having the advantages of "known composition, controlled osmolality and consistency, ease in preparation and storage, and cosat." One must know when to add vitamin and mineral or amino acid packages which are also prepackaged.[32 64] It is becoming more widely recognized that steroids, sedatives, antibiotics and anticonvulsants create an additional need for vitamins.[10]

The fat portion of an IV feeding has often been administered separately, however, at least one study shows excellent results with a mixture of 20% fat emulsion, 8% amino acids, dextrose, electrolytes, vitamins, and trace minerals.[63] It was used from two to thirty-five days with no adverse results.[70] The lipid portion can be useful in insulin resistant patients, decreasing fatty infiltration of the liver, and because it does not increase osmolality of the solution and may decrease (pulmonary diffusion).[12] 20% and even 30% in the IV solution are not uncommon.[50 65]

Complications of intravenous hyperalimentation (IVH) are not uncommon and include mechanical (pneumo-, hemo-, and hydrothorax, arterial or nerve injury, embolism), septic (contaminants in solution or line, sepsis, especially with Staph aureus and Candida, septic embolism and throm-boembophlebitis), metabolic (hyper- and hypoglycemia, hyperammonemia, increased lipids, and deficiencies of essential fatty acids electrolytes, minerals, trace elements, and vitamins). Continuous TPN is associated with less diarrhea than with intermittent. Bolus feedings are discouraged.[34] Only some of the more important deficiency states will be discussed.

Potential Nutrient Deficiencies

Deficiencies of certain nutrients have occurred over the years in association with perioperative nutrition. A review of them reveals interesting information about deficiency states.

Essential Fatty Acids

One of the first deficiencies to be discovered was the essential fatty acids (EFA). In 1972, Caldwell et al described infants on TPN for five or more months; they noted dermatitis, alopecia, thrombocytopenia, and impaired wound healing, all of which improved upon addition of a linoleic acid solution.[66] Other regimens have resulted in increased liver function enzymes, fatty liver and inclusion bodies in hepatocytes, as early as 6-8 weeks after institution of TPN.[12] In addition, Freund has found that an increase in intraocular pressure is a useful early sign in detecting EFA deficiency.[67] This may have relevance to glaucoma. The authors have seen several patients obtain lower intraocular pressures with high dose polyunsaturates.

The optimal amount of linoleic acid is believed to be that which keeps the thri-enoic:tetraenoic ratio less than 0.4; in adults being repleted, this is approximately 4% of total calorie intake.[68]

A deficiency state for linolenic acid has likewise been described by Holman et al who noted neurological symptoms including paresthesia, numbness, inability to walk, leg pain, and blurring of vision. Others have challenged this report.

Phosphate

As with several other nutrients, a deficiency syndrome for phosphate was not discovered unto the 1970's; until this time, TPN solutions had routinely included the anion. With the advent of "new and improved" crystalline amino acid solutions lacking phosphate, however, an acute syndrome of hypophosphatemia was seen to develop within days of starting on TPN.

Lichtman et al,[70] Silvis and Paragus,[71] and Travis et al,[72] all reported acute, marked hypophosphatemia (< 1.0 mg/dl) in patients on intravenous hyperalimentation; they noted decreased 2,3-DPG and ATP (both of which require the anion for phosphorylation) with increased hemoglobin affinity for oxygen and resultant respiratory difficulty. The full syndrome includes paresthesia, muscle weakness, encephalopathy, coma, and death.[32] Deficiency of phosphate is also associated with impaired glycolysis, impaired phagocyte function, hemolysis, rhabdomyolysis, and congestive cardiomyopathy.[73] Since phosphate-free IV solutions have been given for years without development of this syndrome, it is believed the problem is an intracellular shift of phosphate caused by the hypercaloric or anabolic effect of the solution.

Phosphate has a role in intermediary metabolism and in cellular/skeletal structure as phospholipids and hydroxyapatite. Parenteral solutions should provide 0.5-1.0 mmol/kg/day in stable patients without renal failure; serum levels are the optimal way to monitor treatment.[73] Clinicians should be aware of phosphate deficiency caused by excess calcium intake.

Zinc

In 1976, Kay et al described four patients who after approximately two weeks on TPN developed diarrhea, dermatitis, alopecia, and mental depression concurrent with low serum zinc (< 20 mcg/dl, down form 80-150 mcg/dl pre-TPN).[74] They recovered rapidly after zinc supplementation. Fawaz also reported four stressed patients with serum zinc levels between 25-56 mcg/dl; he noted eczematoid dermatitis in all, and decreased hematocrit and albumin in three of the four patients.[75] Arakawa found decreased alkaline phosphate levels associated with subnormal zinc.[76]

Zinc is involved in production of alkaline phosphatase and other enzymes and in protein synthesis. Poor wound healing, impaired immunological function, ageusia, alopecia, acrodermatitis, and anosmia are associated with low levels. There are increased losses of zinc with GI fistulas, diarrhea, zincuria during amino acid infusions, and rapid weight gain.[52 67 73] Supplementation with 2.5 to 4 mg/day in TPn is thought to be sufficient, with an additional 2 mg in acute catabolic states and 6-12 mg with diarrhea or other intestinal losses.[77] It is possible that higher doses of zinc may produce other benefits in surgical patients.

Copper

As with zinc, copper deficiency related to TPN solutions was not discovered until the 1970's when the crystalline amino acid mixtures, now free of several trace elements, were first introduced. Karpel and Peden described an infant on prolonged TPN with markedly low serum copper and Ceruloplasmin. Microcytic hypochromic anemia, hypoplastic bone marrow, retarded bone age, and metaphyseal bone lesions that corrected with copper were seen.[78] Deficiency is also associated with neutropenia and bacterial infection, and normocytic normochromic anemia.[32] Copper is a cofactor of Ceruloplasmin and is involved in the synthesis of oxidative metalloenzymes and elastin. Excreted in bile, these requirements increase with diarrhea, and decrease with liver diseases which block or reduce biliary excretion. Replacement with 0.5-1.5 mg/day is standard.[68]

Chromium

Jeejeebhoy reported a woman in 1977 who presented after three and a half years on TPN with 10% weight loss and peripheral neuropathy with slow nerve conduction. Her glucose tolerance test was abnormal and she had moderate hyperglycemia in the fasting state. Free fatty acids were elevated and her respiratory quotient (RQ) was low. Both serum and hair levels of chromium were low; all symptoms corrected with supplemental chromium.[79]

Chromium is part of the glucose tolerance factor; it is involved in the potentiation of insulin. Standard supplementation is provided in a trace elements package which includes zinc, copper, chromium (10-15 mcg/day) and manganese

(0.15-0.8 mg/day).[23] Chromium's role in sugar metabolism has been confirmed.

Selenium

Although "white muscle disease" (loss of myocytes and replacement with connective tissue) has been recognized in New Zealand sheep raised in selenium-deficient soil, it was not until 1979 that van Rij reported TPN patients with a clinical myopathy that corrected on 100 mcg/day of selenomethionine.[80] An earlier report by Fleming et al in 1976 described a fatal cardiomyopathy culminating in ventricular fibrillation in a twenty-four year old man on TPN for six years.[81]

Selenium is involved in glutathione peroxidase and vitamin E metabolism with a vulnerability to deficiency being associated with low vitamin E levels.[68] Decreased enzyme levels without clinical manifestations were seen by Baptista; replacement with 100 mcg/day of selenium (as selenous acid) improved selenium levels while RBC glutathione peroxidase remained impaired.[82]

Recommendation for standard replacement has been for 0.04-0.16 mg/day as a toxicity syndrome has been described at higher levels. For depleted patients, 200-400 mcg/day is suggested.[73]

Rare Deficiency Syndromes

Other, more rare deficiency syndromes have been reported: molybdenum, with headache, visual disturbances, and mental changes; biotin, with dermatitis, blepharitis, alopecia, and delirium; and carnitine, with jaundice, muscle weakness, and hypoglycemia.[68] These differences point out the need for a complete balance of nutrients from amino acids to trace elements.

Conclusion

Wound healing requires a complete nutritional effort. The nutritional influences on wound healing are approached in humans mostly from the context of overall surgical outcome. Several studies indicate needs for specific nutrients. Many studies were cited correlating poor surgical outcome with poor nutritional status. Determinants for nutritional status are generally agreed to include anthropometric, serum proteins, immune status, nutritional measurements and many other indicators but investigators disagree widely as to which ones serve as the most reliable predictors of surgical outcome. Deficiencies of nutrients once manifested during TPN are now more easily avoided with the addition of more fatty acids, amino acids, vitamins, minerals and trace elements. In the future we expect to identify more nutrients, trace metals, peptides, and oils that need to be added to TPN.

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