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- **Changing Scenario In Clinical Nutrition Practices - then and now**
- **Use of Probiotics: A Continuously Emerging and Growing Concept**

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To Our Readers

The current issue (71) of the Update Series of the Centre for Research on Nutrition Support Systems (CRNSS) consists of two review articles on very different subjects.

The first article written by a surgeon currently in the United States and very well-known internationally for his contribution to the field of clinical and hospital nutrition educates the reader regarding the current practical approach to feeding the hospitalized patient, especially in the critically ill setting and challenges the "standard" practices pertaining to nutritional intervention in the hospital setting which have been in existence for several years. This interesting article draws the attention of the reader to changing concepts in the practice of clinical nutrition from the practical standpoint of not only assessment of nutritional status but also the amount, timing and route of nutrient delivery. The article should serve as an eye opener to all involved in the practice of clinical and hospital nutrition.

The second article on mainly probiotics, but also briefly touching upon prebiotics, discusses the potential beneficial role of probiotics in health and disease and focuses on the importance of probiotics as functional foods and also illustrates the recent Guidelines of the Indian Council of Medical Research (ICMR) for use of probiotics.

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Changing Scenario In Clinical Nutrition Practices - then and now

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Introductory remarks

Over the past several decades, clinicians interested in promoting increased awareness of malnutrition in hospitals have lamented that progress has been slow and frustrating. There seem to be two main reasons for this. First, definitions of malnutrition have been vague and focused more on the community rather than disease- or hospital- based malnutrition. Second, strategies for effective and rapid identification of malnutrition, and immediate initiation of remedial actions, have not been effectively implemented. Organizational structure and discipline, emphasis on adherence to guidelines and good practice patterns were not emphasized. It is only for the past few years that the focus has moved to effective methods of implementation. This write-op will discuss the recent advances in clinical nutrition, urging the reader to discard outdated concepts. The need for practicing clinicians is urgent, as it is unlikely that changes in the educational curriculum for physicians, dietitians and nurses will occur anytime soon. This write-up is applicable for any developing country, although based on experience in India.

New definitions of Malnutrition

The old terms "marasmus" and "kwashiorkor" are no longer used in adult general clinical practice. The use of anthropometric measurements to diagnose and guide nutrition therapy has been abandoned. Although weight continues to be a dependable measure of adequacy of nutritional status, it is not always available for bed-bound patients especially in intensive care units (ICU). Malnutrition in sick patients is a physiological malfunction of several organ systems, mainly due to inflammation (1). However, a clear diagnosis of malnutrition based on inflammation is difficult. Over-nutrition is especially a difficult situation where the patient, family, care-givers and physicians continue to harbor the false notion that an obese patient cannot be malnourished. In fact, muscle loss in sarcopenic obesity is a significant clinical problem but is difficult to detect clinically (2). To this end, an alliance of major societies sought to re-define malnutrition (3). The simplified definition requires 2 of 6 criteria to justify the label of "malnutrition". A diagnosis of malnutrition can be confidently made if 2 out of the following 6 criteria are met: Insufficient energy intake; Weight loss; Loss of muscle mass; Loss of subcutaneous fat; Localized or generalized fluid accumulation; and Diminished functional status. Many of these criteria are subjective, such as bedside assessment of muscle wasting or edema. Subjective assessment has been shown to be useful in many areas of clinical practice such as surgical complications and ventilator management. This is

also true for nutrition where Subjective Global Assessment (SGA) is a proven tool for rapid screening for malnutrition. Many of the commonly used earlier tools for diagnosis of malnutrition have used one or more of the criteria listed above. The new 2015 International Classification of Diseases (ICD) coding provides us with a simpler coding system: E43 Unspecified severe protein-calorie malnutrition (PCM); E44.0 Moderate PCM; E44.1 Mild PCM; E46 Unspecified PCM. For the first time in its history, the coding system has included codes for complications: E64.9 Sequelae of unspecified nutritional deficiencies and E64 Sequelae of PCM (4). Note that the traditional testing for serum visceral protein levels (such as albumin, pre-albumin or transferrin), taught for several decades, have no role to play in current definitions of malnutrition. Their levels rapidly decline in sick patients due to the inflammatory response and not due to "malnutrition" per se and as such measurement of laboratory parameters have neither positive nor negative predictive values.

Addressing malnutrition by providing nutrition therapy

By identifying malnutrition early during the patient's care, and initiating appropriate nutrition therapy, many of the ill effects of malnutrition can be decreased, although it is obvious that they cannot be negated entirely. An urgent need to address malnutrition in hospitals has been identified and remedial measures suggested by calling to action an interdisciplinary approach involving all parties. These approaches and the rationale for providing evidence-based nutrition therapy to malnourished patients have been well elucidated (5).

Ill effects of Malnutrition as evidenced by 30-day hospital readmission rates

30- day readmission rates are used currently as a reliable surrogate marker for quality of cost-effective medical care. This marker may not be suitable for clinical studies conducted in India as many patients opt to stay in the hospital even after reasonable recovery and being fit for discharge, due to the difficulty in finding affordable short-term accommodation close to the hospital. This is especially true for patients from rural areas, where the distance to good health care and facilities for transportation are suboptimal. Nevertheless, there has been a spate of recent publications using 30- or even 90- day readmission rates and efforts to decrease them (6, 7). In the USA, the government has mandated that readmission rates must be decreased or else hospitals face stiff penalties and fines (8).

Predictive formulas versus "rules of thumb"

Although clinicians focus on exact calorie requirements, evidence suggests that "one size does not fit all". There is great individual variability in calorie requirements especially in critically ill patients. Predictive equations, although popular with tech-savvy clinicians using mobile Apps, have been shown to be of little use (9). A general rule of thumb is to aim for 25-30 kcal/kg of ideal or adjusted body weight. Formulas for obese individuals are different. The emphasis is now on protein requirements, aiming for up to 2 g/kg/day (10). The

Harris-Benedict equation, still taught in our colleges, was published decades ago and not accurate for clinical use. During the early days of nutritional support, a popular term was "hyperalimentation" implying that more than needed calories were administered. This is an obsolete term and no longer relevant. The detrimental effects of overfeeding including refeeding syndrome are well recognized.

The importance of oral nutritional supplements (ONS)

The benefits or oral nutritional supplements in the community and hospitalized patients in general are being recognized more recently. ONS decreases complications, especially infections, decreases hospital and ICU length of stay, facilitates early ambulation, with significant benefits of decreasing cost (11, 12). Quality of life improves. ONS administered for 7–10 days prior to surgical procedures results in better outcomes. Select groups of patients such as the elderly and those with malignancies are especially vulnerable to the effects of malnutrition and benefit from ONS.The benefits of ONS in decreasing 30-day readmissions has also been demonstrated and is an extremely cost-effective method of decreasing complications (13). Early detection of malnutrition soon after hospitalization, immediate provision of ONS, on-going educational measures for the patient, care givers, and health care providers (especially physicians), along with attention to discharge planning and instructions, benefit the patient and has positive effects on health care economics. ONS is not simply any commercially available product. The market is flooded with products claiming to improve nutrition, with false advertising in the media. ONS are actually nutritional pharmaceuticals, or "nutracueticals" and should be clearly defined as a medical food; they are scientifically designed formulations with the correct proportion and form of macronutrients, with adequate and bioavailable micronutrients.

Micronutrients

In the past, clinicians have concentrated more on macronutrients, whilst delegating micronutrients to a secondary role of an academic curiosity and rarity in today's environment. The term "micronutrient" includes both vitamins and trace elements, the essential trace elements being zinc, selenium, copper, chromium and manganese. After the advent of enteral and parenteral nutrition therapy, the important roles that micronutrients play has been better appreciated. Detailed reviews of the importance of micronutrients are available elsewhere (14, 15). Deficiencies of every micronutrient has been recognized in clinical practice, compounded by various interactions between themselves, and with medications. Micronutrient deficiency is also recognized as a form of malnutrition. If left uncorrected, these deficiencies may lead to disastrous consequences including death. Example include: thiamine deficiency as a cause of unexplained metabolic acidosis, selenium deficiency causing myositis and cardiomyopathy, zinc deficiency affecting the function of several key enzymes, etc. A high index of clinical suspicion is needed as routine laboratory testing is not required, and is not cost or time-effective.

Bowel sounds and oral intake

Bowel sounds and passage of flatus are not needed to initiate enteral feeding, either orally or through feeding tubes. This information has been available for over 2 decades, yet not practiced. The 2016 guidelines have re-emphasized this concept (16, 17). A patient centric approach is recommended allowing the patient to consume oral diet, in liquid or solid form, and of his/her own choice. There is no role for specialized unpalatable oral diets during the postoperative period when oral intake has to encouraged to facilitate wound healing (18). Guidelines clearly state that the presence of a gastro-intestinal anastomosis is not a contraindication for oral or enteral feeding, yet this outdated practices continues. Physician-directed malnutrition has to be avoided (19). Acute pancreatitis is no longer a condition requiring routine nil by mouth orders. Even patients with "open abdomens" can be safely fed with enteral feeding. The 2016 American Society for Parenteral and Enteral Nutrition guidelines (17) as well as Enhanced Recovery after Surgery (ERAS) guidelines (20) clearly state that most patients can tolerate a regular diet during the immediate postoperative period as their first meal. Intra-jejunal feeding is reserved for the rare occasion when adequate intra-gastric feeding is not possible. Its use has decreased considerably over the years. The pre-emptive use of prokinetic agents (metoclopramide) in critically ill patients receiving enteral feeding is also encouraged (17).

Gastric residual volume measurements

Although still practiced extensively, measurement of gastric residual volumes during intra-gastric tube feeding, has been shown to have little practical utility. Strong recommendations have been made not to measure GRV on a routine basis. This may be justifiable on conditions of delayed gastric emptying, such as diabetic gastroparesis. If GRV is measured for any reason, one can liberalize interpretation of what constitutes an excessive volume and accept volumes of 400 to 500 mL. Enteral feeding should not be decreased or discontinued due to a false perception of what is excessive (17).

Enhanced Recovery After Surgery (ERAS) Protocols

ERAS protocols, initiated in Scandinavian countries, is now spread throughout the world (21).
A multidisciplinary approach to peri-operative care, including the pre-, intra- and postoperative periods is emphasized. Nutritional assessment is a crucial component with correction of deficiencies prior to any major surgical procedure (22). This also includes normalization of electrolyte levels, including magnesium and phosphorus, not routinely checked previously. The practice of starving patients for several hours prior to general anesthesia has been abandoned. In fact, patients are given a carbohydrate rich drink 2 hours prior to surgery; this repletes the hepatic and muscle glycogen stores and decreases stress response and postoperative hyperglycemia. Epidural anesthesia is encouraged, minimizing the systemic use of narcotics, and thereby decreasing postoperative ileus, and nausea, leading to early resumption of enteral feeding with it's well-known benefits. ERAs protocols form an integral part of the nutritional care of the patient. Further information is available from the ERAs website (20).

Blenderized kitchen prepared diets: No place in today's hospitals

A widely practiced method of feeding patients is the outdated use of kitchen prepared blenderized diets. The reader may be amused to know that a search for these key words will result in few hits in the medical literature and this practice has been abandoned decades ago. It has been known for years that blenderized diets are of unknown composition, with wide variations between the expected and actual composition (23, 24). Although this has been shown for macronutrients, it is likely to be true for micronutrients too. The high viscosity requires the use of large bore feeding tubes with resultant complications such as maxillary sinusitis, esophageal and gastric erosions, and gastro-esophageal reflux. The bacterial contamination of blenderized diets is especially worrisome (25). Within 4 hours of transfer to the patient's bedside, the bacterial content would have increased to dangerously high levels. Acid suppressant medications, commonly administered to patients although not always indicated, make matters worse. Health care providers, and family members, often consider the cost of the ingredients alone and come to the erroneous conclusion that kitchen-prepared diets are less expensive. However, this is not true if one considers the cost of procurement, preparation, transport, wastage, and complications. Individual institutions are advised to perform their own cost-analysis. In short, there is no role for kitchen-prepared diets in today's hospitals.

Disease specific formulas

In the majority of cases, standard enteral formulas can be used for feeding. Elemental or semi-elemental (or oligomeric) formulas are reserved for the rare patient where all attempts to increase tolerance have failed. There is no role for pulmonary or hepatic formulas (17). Diabetes-specific and renal formulas have a definite role in specific situations.

Parenteral nutrition

During earlier days of nutrition support, parenteral nutrition was the buzz word; the concept itself was novel. With the realization that enteral nutrition has far greater benefits than its nutrient content, especially in its effect on gut immunity, the use of parenteral nutrition has slowly declined. Its use is limited to those patients where attempts to optimize enteral feeding have failed for 5 to 7 days. Non-functioning gut or high output fistulas require parenteral nutrition as supportive therapy.

Team approach and changes to hospital-wide systems

Success in implementing better nutrition care practices involve six principles (5): Create an institutional culture, Redefine clinicians' roles to include nutrition, Recognize and diagnose all patents at risk, Rapidly implement interventions and continued monitoring Communicate nutrition care plans and Develop discharge nutrition care and education plan. A team-based approach has been successful in the management of other medical conditions such as

hypertension, cardiac failure and diabetes. Its role in nutritional support too is well established. Once a culture of sensitivity to nutrition-related issues has been created in an institution, on-going educational programs enhance the effectiveness of subsequent initiatives. Each member of the team has specific and general job descriptions, but the detection of malnutrition, and the provision of timely and scientific nutrition therapy is the responsibility of everyone. The term "systems engineering" commonly used in industry, is also applicable to health care.

Concluding remarks

This brief review highlights the need for physicians, all health-care providers and especially hospital administrators, to include nutrition therapy as an integral part of patient care. This includes special attention to preoperative care (26). Such attempts are being made in other parts of the world (27) and it is about time that we too in India accept this approach at individual and institutional levels.

Web-based resources

www.nutritioncare.org (American Society of Parenteral & Enteral Nutrition)
www.espen.org (European Society of Parenteral and Enteral Nutrition)
www.nice.org (National Institute of Clinical Excellence)
www.sccm.org (Society for Critical Care Medicine)
http://nutritioncareincanada.ca (Canadian Malnutrition Task Force)
www.criticalcarenutrition.com

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Use of Probiotics: A Continuously Emerging and Growing Concept

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1. Origin and History

The intestine's normal microflora is a metabolically active but as yet unexplored organ of host defense. It is estimated that the human microbiota contains as many as 1014 bacterial cells, a number that is 10 times greater than the number of human cells present in our bodies [1, 2]. The large intestine contains 300–500 different species of bacteria [3]. Some of these are potential pathogens and cause infection under certain circumstances. Microbial colonization of the intestine begins after birth, and the development of the normal flora is determined by contact with the maternal intestinal flora and surroundings, and possibly by genetic factors [4, 5]. It is thought that those who are breast-fed have a natural predominance of bifidobacteria, while formula-fed infants have a more complex "microflora" similar to that in the adults. After weaning, however, the composition of the microflora gradually alters to resemble adult microflora [6, 7].

Elie Metchnikoff first postulated that lactic acid bacteria (LAB) offered health benefits capable of promoting longevity. The term "probiotics" was first introduced in 1965 by Lilly and Stillwell; in contrast to antibiotics, probiotics were defined as microbially derived factors that stimulate the growth of other organisms. In 1989, Roy Fuller emphasized the requirement of viability for probiotics and introduced the idea that they have a beneficial effect on the host. Probiotics are defined as 'live microorganisms which when administered in adequate amounts confer a health benefit on the host' [8]. Certain strain of bacteria have been discovered over the years to have probiotic properties, mainly consisting of lactic acid producing bacteria lactobacilli, streptococci, enterococci, lactococci, bifidobacteria), Bacillus and fungi such as Saccharomyces and Aspergillus.

Lactic acid bacteria, including Lactobacillus species, which have been used for preservation of food by fermentation for thousands of years, can serve a dual function by acting as agents for food fermentation and, in addition, potentially imparting health benefits. Strictly speaking, however, the term "probiotic" should be reserved for live microbes that have been shown in controlled human studies to impart a health benefit.

Box 1- ICMR Guidelines for evaluation of probiotics

- **Identifying the strain** and linking its specific health effect as well as to enable accurate surveillance and epidemiological studies. Nomenclature of the bacteria must conform to the current, scientifically recognized names as per the International Committee on Systematics of Prokaryotes (ICPS)
- The following **in vitro tests** with standard methodology are recommended for screening putative probiotic strains: Resistance to gastric acidity, Bile acid resistance, Antimicrobial activity a gainst potentially pathogenic bacteria, Ability to reduce pathogen adhesion to surfaces, Bile salt hydrolase activity
- **In vivo safety studies in animal models** : Assessment of the acute, subacute and chronic toxicity of ingestion of extremely large amounts of probiotics should be carried out for all potential strains.
- **In vivo efficacy studies in animal models** : To substantiate in vitro effects, appropriate, validated animal models must be used first, prior to human trials.
- **Evaluation of safety** : Determination of antibiotic resistance patterns. It should be ascertained that any given probiotic strain is not at significant risk with regard to transferable antibiotic resistance, Assessment of undesirable side - effects, If the strain under evaluation belongs to a spec ies that is a known mammalian toxin producer or of hemolytic potential, it must be tested for toxin production and hemolytic activity respectively.
- **Evaluation of efficacy** : The principal outcome of efficacy studies on probiotics should be proven with simila r benefits in human trials, such as statistically and clinically significant improvement in condition, symptoms, signs, well -being or quality of life, reduced risk of disease or longer time to next occurrence or faster recovery from illness. Each of the parameter should have proven correlation with the probiotics tested. Probiotics delivered in food may not be tested in Phase 3 studies (effectiveness), unless the **product makes a specific health claim**
- **Effective dosage** : The minimal effective dose or the level of viable cells of the probiotic strain in terms of cfu/ml/day in the carrier food that demonstrates general health promoting functions or well being or specific health claims in target population should be clearly indicated.
- **Labeling Requirements:** Genus, species and strain designation following the standard international nomenclature, The minimum viable numbers of each probiotic strain should be specified at the level at which efficacy is claimed and at the end of shelf- life, Evidence-based health claim(s) should be clearly stated, The suggested serving size to deliver the minimum effective quantity of the probiotic related to the health claim and proper storage conditions to be mentioned.
- **Manufacturing and Handling:** Adequate quality assurance programmes should be in place. Good Manufacturing Practices should be followed in the manufacture of probiotic foods. The Codex General Principles of Food Hygiene and Guidelines for Application of Hazard Analysis and Critical Control Point (HACCP) (40) should be followed.

ICMR-DBT Guidelines, 2011

2. Selection, Safety and Guidelines

Probiotics are well-known for their role in modulating a healthier gut. Now, probiotics are found to exert other health advantages such as improving lactose intolerance, positively influencing intestinal flora, reducing inflammatory or allergic reactions, reducing clinical manifestations of atopic dermatitis, Crohn's disease, diarrhea, constipation, candidiasis, and urinary tract infections, competitively exclude pathogens, increasing humoral immune responses, biotransformation of isoflavone phytoestrogen to improve post-menopausal symptoms, bioconversion of bioactive peptides for anti-hypertension, and reducing serum cholesterol level [9-12].

Considering this impressive list of potential health-promoting benefits, it is not surprising that there continues to be considerable interest in the use of probiotics as biotherapeutic agents. Before a probiotic can benefit human health it must fulfill several criteria: it must survive passage through the upper gastrointestinal (GI) tract and arrive alive at its site of action. It must be able to function in the gut environment and also have good technological properties so that it can be manufactured and incorporated into food products without losing viability and functionality or creating unpleasant flavors or textures. The theoretical basis for the selection of probiotic micro-organisms including safety, functional and technological aspects.

Lactobacilli and Bifidobacteria have been rarely associated with human clinical infections which are likely to be a result of opportunistic infections especially in immune-compromised individuals [13, 14]. Many probiotic strains in use for several decades have been validated for their safety and efficacy and are therefore, safe to use [15, 16].

ICMR has laid down Indian guidelines for evaluation of probiotics in food in India after taking into consideration guidelines available in different parts of the world [17]. The guidelines deal with the use of probiotics in food and provide requirements for assessment of safety and efficacy of the probiotic strain and health claims and labeling of products with probiotics as illustrated in Box 1.

3. Health claims

Probiotics are intended to assist the body's naturally occurring gut microbiota. Some probiotic preparations have been used to prevent diarrhea caused by antibiotics, or as part of the treatment for antibiotic-related dysbiosis. Studies have long documented probiotic effects on a variety of gastrointestinal and extraintestinal disorders, including inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), diarrohoea, vaginal infections, anti-oxidative effects, reduction of allergic symptoms, lactose intolerance and immune enhancement [18-20]. Some of the upcoming health claims shown by a number of probiotics are as follows-

a) Type 2 Diabetes Mellitus and Obesity- One study in an adult population with type 2 diabetes [21] has shown that their gut microbiota differs from that of non-diabetic adults, and that health may potentially improve when the gut microflora is modified by the administration of probiotics and prebiotics. The population of Bifidobacteria (and most other organisms in the group of Firmicutes) is slightly lower in individuals with obesity than in lean people [22]. A similar finding was reported in patients with type 2 diabetes mellitus in comparison with non-diabetic patients [23]. Obese individuals when administered Lactobacillus acidophilus NCFM and Lactobacillus gasseri SBT2055 showed a decrease in fat mass and the risk of Type 2 Diabetes Mellitus and insulin resistance [24, 25]. In the active group which consumed L. gasseri, abdominal, visceral, and subcutaneous fat areas decreased significantly. Body weight also decreased significantly. Clinical trials using prebiotics like arabinoxylan [26, 27] and inulin-type fructans [28] have shown positive results in diabetic, overweight, and obese populations.

b) Cancer Prevention- In a double blind study with 138 patients, the probiotic strain L. casei Shirota was shown to have a preventive effect on the recurrence rate of superficial bladder cancer after surgery. In the long term, the tumor incidence in the large intestine [29] and in other organs (breast cancer in rats and mice, metastases in the lung [30] was lowered by adding 5 - 15% inulin or oligofructose to the diet. This effect was even more pronounced when a combination of prebiotics and probiotics was given [31]. Xylooligosaccharide was shown to reduce the number of aberrant crypt foci in the colon of 1, 2-dimethylhydrazinetreated male Sprague-Dawley rats [32].

c) Atopic Dermatitis- Children suffering from atopic dermatitis (AD) have higher number of S. aureus and Clostridium in their colon and lower number of Enterococcus, Bifidobacterium, and Bacteroides [33, 34]. When Lactobacillus GG was administered to high risk infants, there was a 50% reduction in observed atopic eczema [35]. In another study in Finland when children were given a whey formula with L. rhamnosus or B. animalis ssp. lactis for 2 months, the skin condition improved [36]. Supplementation with L. rhamnosus HN001 in pregnant women and their newborn infants substantially reduced the cumulative prevalence of eczema in infants [37]. . A double blind, randomized, placebo-controlled intervention in children with atopic dermatitis (AD) using Danisco's probiotic strain Bifidobacterium animalis subsp lactis. Bi-07 showed that there was a significant reduction in the severity of AD with an improved ration of IFN-γ and IL-10 [38].

d) Hypocholesterolemic and Hypotensive Effects- In vitro studies conducted previously have evaluated a number of mechanisms proposed for the cholesterol-lowering effects of probiotics and prebiotics. One of the purported mechanisms includes enzymatic deconjugation of bile acids by bile salt hydrolase of probiotics. Cholesterol was also removed by probiotics by incorporation into the cellular membranes during growth [39]. The

hypocholesterolemic effect of the probiotics has also been attributed to their ability to bind cholesterol in the small intestines. Studies with humans have shown similar results. In a 10-week randomized, double-blind, placebo-controlled, crossover study with L. acidophilus L1 milk, there was a significant reduction in serum cholesterol compared to the placebo group [40]. Xiao et al. [41] evaluated the effects of a low-fat yogurt containing B. longum BL1 in a randomized, single blind, placebo-controlled and parallel study involving thirty-two patients. At the end of 4 weeks, the patients showed a significant decline in total serum cholesterol, LDL-cholesterol and triglycerides. There was also a 14.5% increase in HDL cholesterol when compared to the control. However some controversial results have also been observed. Double blind, randomized, and crossover studies using L. rhamnosus LC705 [42], parallel design studies using L. fermentum [43], and crossover studies using L. acidophilus [44] showed no change on serum lipids, triglycerides, or cholesterol. It has also been demonstrated that probiotics and their products can positively influence blood pressure through mechanisms which also result in improving total cholesterol and low-density lipoprotein cholesterol levels, reducing blood glucose level and insulin resistance, and by regulating the renin–angiotensin system [45-47].

e) Renal Health- Simenhoff et al. demonstrated that hemodialysis patients who were fed L. acidophilus NCFM had significantly lower blood dimethylamine and nitrodimethylamine levels [48, 49]. In a 6-month randomized, double-blind, placebo controlled, and cross-over trial conducted in four countries and including a total of 46 patients with chronic kidney disease CKD stage 3 and 4, BUN levels decreased in 29 patients ($P < 0.05$), creatinine levels decreased in 20 patients (no statistical significance), and uric acid levels decreased in 15 patients (no statistical significance). Almost all subjects reported having experienced a substantial perceived improvement in their quality of life ($P < 0.05$) [50, 51].

f) Hepatic Encephalopathy- Hepatic encephalopathy is a dreaded liver disease. Minimal encephalopathy is a condition of chronic liver disease with no clinical symptoms of brain dysfunction. When patients with minimal hepatic encephalopathy were given Bifidobacterium longum with fructooligosaccharide for 9 weeks, their cognitive functions were seen to improve [52]. Minimal hepatic encephalopathy (MHE) is a complication of cirrhosis during which accumulation of neurotoxic substances in the bloodstream produces neurological manifestations. When MHE patients were given a synbiotic preparation of probiotics and prebiotics, the MHE was reversed in 50% of the patients, and this effect was accompanied by a significant increase in Lactobacilli [53].

g) Dental Caries- The impact of oral administration of probiotics on dental caries has been studied in several experiments utilizing different test strains. Lactobacillus rhamnosus GG and L. casei have proved their potential to

hamper growth of oral streptococci [54, 55]. Studies showed in a placebo-controlled randomized double blind intervention study that the administration of probiotics lactobacilli (LGG) to kindergarten children in Helsinki, Finland, resulted in reduction of their caries risk and initial caries development [56].

4. Conclusion

As the gut microbiota appear to contribute to nearly every aspect of the host's growth and development, it is not surprising that a number of diseases have been associated with an imbalance in either composition, numbers, or habitat of the gut microbiota. Diet is a major focus of public health strategy aimed at maintaining optimum health throughout life, preventing early onset of chronic diseases such as gastrointestinal disorders, cardiovascular disease, cancer, osteoporosis, as well as promoting healthier ageing. The growing demand for 'healthy' foods is stimulating innovation and new product development in the food industry internationally. The food industry has a central role in facilitating healthier eating practices through the provision and promotion of healthy foods. Probiotics, prebiotics and synbiotics have emerged as potential functional foods for a large number of gastrointestinal disorders such as IBD, diarrhea, colo- rectal cancers and also as immune modulators, cholesterol lowering agents, potential beneficial effects in hypertension, Type 2 Diabetes Mellitus and obesity. The future of probiotics appears promising but more human trials with greater sample size need to be designed and conducted to establish a strong and consistent relationship.

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