NUTRITION INFORMATION CENTRE
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PROBIOTICS AND PREBIOTICS:
GRANNY'S WISDOM TAKES US BACK TO THE FUTURE

The information explosion in the science of nutrition very often creates the impression that available information is contradictory. Consequently, it is no longer easy to distinguish between fact, misinformation and fiction. The Nutrition Information Centre of the University of Stellenbosch (NICUS) was established to act as a reliable and independent source of nutrition information.

Food, "glorious food", has always been, and continues to be, the subject of intense debate among the public and media alike, which is not really surprising bearing in mind the central role food plays both in the every day life of all people and, in the longer term, on their overall health. Over the years many tales have been passed down generations extolling the benefits of specific foods, "carrots are good for the eyes", "fish is good for the heart", "vegetables and roughage is good for the gut" "yoghurt is good for the skin", to mention but a few. The science of Nutrition is beginning to understand and add weight to some of these tales. The growth of knowledge in nutrition together with the growth and developments in food technology is transforming our concept of food from one of being necessary to give us energy and nutrients for our daily tasks and to prevent the traditional nutrient deficiencies, to one of the reason(s) and mechanism(s) by which certain foods are reported to be associated with a reduced risk of chronic diseases.

The clearly emerging, but still to be fully understood, probiotics and prebiotics era over the past number of years is another such example, which forms the subject of current debate and intense research. The emergence of the probiotics concept can be attributed to the observation at the turn of the century that the long and generally healthy life of some peasants in Bulgaria was due to their consuming fermented milk products.

The use of fermented milk products, in the form of yoghurt for example, is of course not new. Many populations in the African continent and the world have used it as a means of preserving milk successfully and safely, over many decades. What is new though is the apparent importance of some specific microorganisms used in the fermentation of such products in relation to the potential beneficial effects on gastrointestinal function, the type of microorganisms that are normally found in the gastrointestinal tract, and the effect of such microorganism may have on overall health and well-being in general. What is often insufficiently appreciated is that there are literally hundreds of species of microorganisms that are normally present in our gastrointestinal tract. For perspective, it has been estimated that bacterial populations in the normal human body can be as high as 100, 000, 000, 000, 000 cells, which is actually 10 times higher than the number of human cells in the whole body. Gastrointestinal microflora consists of more than 500 different species of bacteria, which coexist in the human gut. The composition of the microflora changes throughout the intestinal tract, with the highest microbial activity being in the colon. The establishment and maintenance of the healthy bacteria in the gut is a complex and multifactorial process, which is not fully understood. Colonisation of the gastrointestinal tract of newborn infants starts immediately after birth and occurs within a few days. Initially the type of delivery (birth canal versus caesarean section) and diet might affect the colonization pattern. Other environmental factors also have a role to play since differences exist between infants born in developing countries and those born in developed countries, and also between infants from different hospital wards. Initial colonization is very relevant to the final composition of the permanent flora in adults. It has also been found that the species vary greatly between individuals.

MAIN FUNCTIONS OF GUT FLORA

1) Metabolic

Gut microflora are responsible for the fermentation of non-digestible dietary components (resistant starches, cellulose, hemicellulose, pectins, gums), resulting in the formation of short-chain fatty acids (SCFA). In the host, fermentation leads to the release of energy and absorbable substrates, whilst bacteria derive energy and nutritive products for growth and proliferation. Bacteria in the colon also play a role in the synthesis of Vitamin K and B vitamins and in the absorption of calcium, magnesium and iron.

2) Trophic

A very important function of SCFA is the proliferation and differentiation of the intestinal lining. Gut flora also play an important role in the development and maintenance of immune function, since the intestinal mucosa is the main barrier between the immune system and the external environment. Thus, gut flora are thought to play an important role in maintaining the health of both the gut and the body function.

3) Protective

Gut microflora serve as a line of resistance and prevent the invasion of tissues by pathogenic bacteria (disease-causing).

WHAT IS A PROBIOTIC?

The term probiotics refers to specific live microorganisms in a food or a supplement that survive the passage through the gut, improve the microbial balance in the large bowel and are thought to have beneficial effects on the host, the human body. Probiotics do not usually colonise the human intestine. Probiotics are marketed as capsules, tablets, milk, fortified infant milk formulas, yoghurts and other dairy products as well as powders. Examples of such microorganisms include *Lactobacillus rhamnosus GG, Lactobacillus acidophilus and Bifidobacterium bifidum*. It is well known that the effect of a bacterium is strain specific and cannot be extrapolated even to other strains of the same species.

WHAT IS A PREBIOTIC?

The term generally refers to a food component that cannot be digested in the gut but has potentially beneficial effects on the host by selectively promoting the growth/activity of a number of microorganisms in the large bowel, such as *bifidobacteria* and *lactobacilli,* which are thought to have potential health promoting effects.

Efforts to fully understand the role of probiotics and prebiotics in human health have intensified over the last decade, primarily because of the realization that gut immunity decreases with age, exposure to antibiotics may have detrimental effects on the balance of microorganisms in the large bowel including the emergence of disease causing microorganisms as well as the potential beneficial effects of probiotics and prebiotics in reducing the risk for chronic disease. The totality of the currently available evidence on these and other related issues ranges from the established and generally accepted beneficial effects on health to the promising clarification of the underlying mechanisms of benefit, to the anecdotal, and often irresponsible, claims of benefits. Clearly, on-going intensive research in the field will put better perspective on many outstanding issues and claims.

WHAT IS A SYNBIOTIC?

A synbiotic can be defined as a mixture of probiotics and prebiotics which beneficially affects the host by improving the survival and establishment of the beneficial live microorganisms (found in the dietary supplement) in the gut, by stimulating the growth of these microorganisms in the gut, and/or by activating the metabolism of health-promoting bacteria, resulting in the improvement of host welfare. Synbiotic products have the potential to enhance health but require further investigations in humans, in order to establish scientifically sound recommendations.

BENEFICIAL EFFECTS OF PROBIOTICS ON HEALTH

Probiotics have been increasingly included in human diets because of their potential health benefits. These include the improved digestion of lactose in food, improved resistance to disease causing microorganisms found in the gut, the improvement of blood cholesterol in relation to heart disease, the prevention of cancer, bacterial overgrowth in the small bowel as well as allergies, urogenital infections and hypertension, and the improvement in immune function. For the purpose of this information leaflet only those with sufficient or interesting emerging scientific basis will be discussed briefly. Although some evidence is available for other claims attributed to the consumption of probiotics, the available data cannot be considered as substantial and needs to be confirmed. Many potential mechanisms have been suggested to explain the proposed associations between micoflora and human health, but only a few have been well established.

♦ Lactose intolerance

Although it is true that this disorder can be a real and unpleasant problem for some people, it is equally true that this disorder has been overemphasized. For perspective the available evidence has consistently confirmed that the vast majority of a given population tolerates a cup of milk a day without any side effects. For those that are truly intolerant to lactose and do like dairy products, fermented dairy products (yoghurt, cheeses) improve lactose tolerance and reduce the symptoms of intolerance. The mechanisms by which lactose tolerance is improved include:

- the presence of microbial lactase in fermented milk products, which acts on ingested lactose and relieves symptoms of intolerance, and
- the reduced intestinal transit time of yoghurt, which allows for the more complete digestion of lactose

The principal bacteria found to have beneficial effects on lactose tolerance in adults are lactobacilli and bifidobacteria.

♦ Urinary tract infections in woman

Urinary tract infections are ascending infections caused by bacteria in the stool and dietary changes can affect the bacterial flora involved. A recent case-control study reported that women who frequently consume fermented milk products containing probiotic bacteria, such as *Lactobacillus acidophilus* or *Lactobacillus GG*, experience fewer urinary tract infections. Dietary guidance may therefore be the first step towards preventing urinary tract infections in women. Other studies have also reported a significant reduction in the recurrence of urinary tract infections following the regular urogenital use of probiotic capsules.

♦ Gut function

One of the microorganisms used in probiotics, especially in dairy products, which has been extensively studied in adults and children is *L.actobacillus rhamnosus GG*.

♦ Traveller's Diarrhoea:

Traveller's diarrhoea is caused by a diverse, ever changing range of microbial pathogens, including pathogenic *Escherichiacoli, Salmonella, Campylobacter* and *Shigella* strains as well as viruses. It is very therefore difficult to identify a specific probiotic strain, which is protective against traveller's diarrhea, and thus unlikely that one probiotic strain will inhibit such a broad spectrum of pathogens.

♦ Infantile Diarrhoea:

Lactobacillus rhamnosus GG has been consistently shown to reduce the duration of acute infantile diarrhoea, often the result of a rotavirus infection, by about 50%. This strain has also been useful as a prophylaxis of diarrhoea in undernourished children, especially in infants who are not breastfed. The underlying mechanisms for the beneficial effect are thought to include the stimulation of the immune response and/or the enhancement of the gut mucosal integrity. Additionally, *Bifidobacterium bifidum*, given in conjunction with *Streptococcus thermophilus* in a standard milk formula, has been shown to reduce the incidence of rotaviral diarrhoea. Other studies in children with gastroenteritis who received a probiotic supplement (either *Lactobacillus rhamnosus*, *Lactobacillus reuteri* or *Lactobacillus casei*) have also shown a significant decrease in the duration of diarrhoea in these children.

In the developing world of course, diarrhoea is one of the leading causes of child morbidity and mortality and although probiotics are thought to have an important role to play in its prevention, their value must be more extensively confirmed.

♦ Antibiotic Associated Diarrhoea:

Probiotics have been used to prevent antibiotic associated diarrhoea, which is a common adverse effect of antibiotic therapy. Antibiotic associated diarrhoea results from the disturbance of the normal microflora in the gut by the antibiotics, which enables overgrowth of microorganisms that cause diarrhoea. It is also thought that the diarrhoea may be the result of a decrease in the metabolism of bile acids and carbohydrates. S*accharomyces boulardii* non-pathogenic yeast) and *lactobacilli* have been reported to be potentially beneficial. There is however still little consistent evidence to support the use of probiotics in the treatment of antibiotic associated diarrhoea. *Nevertheless, Lactobacillus rhamnosus GG* has been reported to reduce the incidence of diarrhoea, nausea and taste disturbances in patients receiving rabeprazole, clarithromycin and tinidazole ('triple therapy') for *Helicobacter pylori* eradication. Similar results have also been observed with other probiotics including *L*actobacillus acidophilus, *Lactobacillus johnsonii*, *bifidobacteria* and *S*treptococcus *boulardii.*

♦ Helicobacter pylori gastritis

Helicobacter pylori is a microorganism that is known to cause gastritis and peptic ulceration and has been implicated in the pathogenesis of both gastric cancer and lymphoma. A recent study reported that a mixture of probiotic organisms (including Lactobacillus bulgaricus, Lactobacillus acidophilus and Bifidobacterium lactis) was associated with a significant reduction in Helicobacter pylori infection over a period of 6 weeks in adults. Similarly probiotic formulations (Two Lactobacillus species) administered over a 4-week period, significantly reduced Helicobacter pylori activity in asymptomatic children. This preliminary evidence appears promising, but it is important to remember that not all previous studies have found therapeutic effects, and further studies are needed before probiotics can be recommended for the prevention and treatment of Helicobacter pylori infection.

♦ Inflammatory Bowel Disease (IBD), Irritable Bowel Syndrome (IBS) and Colorectal Cancer (CRC):

Probiotics have also been studied for their role in the management of chronic disease states such as IBD (Crohn's disease, Ulcerative Colitis) and IBS as well as the prevention of CRC. Probiotics, either through regulation of the inflammatory response or modulation of the gut microbial composition and/or activity, might bring about relief in IBD symptoms or maintain remission. The strain, *Escherichia coli Nissle* 1917, has been shown to be effective in preventing relapse in Crohn's disease patients. *Saccharocmyces boulardii* has also been shown with a measure of success to be useful in relieving the symptoms of active Crohn's disease. Additionally, current evidence suggests that lactic-acid producing bacteria have modest clinical benefits and are safe for use in IBD patients. However, placebo-controlled double-blind studies in IBD, active and inactive, which control for the effect of other concurrent medical therapy of the disease are needed before recommendations can be made on the routine use of probiotics in IBD. Information on dose, duration of treatment and properties of various strains for different clinical indications is also necessary.

The causes of IBS are indeed diverse and depletion of gut microflora has been added to the list of contributory factors. However, the ability of probiotics to impact beneficially on the IBS symptoms remains to be proven and there is a need for further intervention studies with a broader range of probiotic strains.

Although the predisposition to developing CRC is known to be partially associated with the genetic background of the individual (approximately 35%), non-hereditary environmental factors are also thought to be very important. In this regard, diet and its interaction with the gut flora, together with the age associated decrease in immune function is the subject of intense investigation. Epidemiological studies suggest that fermented dairy products, usually yoghurt, might reduce the

risks of adenomas in the colon. Colonic flora would appear to be a major environmental factor, which could beneficially modulate CRC risk, but it still remains to be conclusively shown that probiotics do afford such protection against CRC.

♦ Immune function

The mucosal lining of the gut acts as a barrier to antigens and other chemicals derived from food and also from the microorganisms that are normally found in the gut. It has been estimated that the lining of the gut has a surface area of some 300 square meters, which is the largest body area in direct contact with the environment. This barrier forms the first line of defense of the body and regulates how the body responds to a particular ingested foreign substance. The working of the barrier depends on the integrity of the mucosal lining of the gut, which determines how effective this component of the immune system functions

The movement of bacteria from the gastrointestinal tract through the mucosal barrier, when defences fail, is called bacterial translocation. After crossing this barrier, bacteria can travel via the lymphatic system to other sites in the body, producing sepsis, shock, multisystem organ failure or death. Bacterial translocation can occur in humans during various disease settings. Probiotics have been shown to enhance these lines of defense by a variety of mechanisms including an increase in the levels of various immunoglobulins, especially secretory IgA, and through the enhancement of phagocytic activity of circulating leucocytes. It is postulated that gut microflora elicit an immune response at both local and systemic levels. In a recent study, a *Bifidobactrium lactis* HN019 strain enhanced non-specific immune function (namely, leucocyte proliferation, increased phagocyte production and proinflammatory cytokine production). Several other studies have confirmed the beneficial role of *Bifidobacterium lactis* HN019 on immune response in healthy adults. However, despite these interesting and encouraging findings a number of issues that relate to the clinical significance in terms of long-term outcomes remain to be elucidated.

♦ Infant health

Probiotics are consumed as food by many children and the tolerance and safety of long-term consumption of specific types and strains of bacteria has not been well documented. A recent study investigated the long-term tolerance and safety of the consumption of infant formulas containing live probiotic bacteria (Bifidobacterium lactis and Sterptococcus thermophilus). Healthy infants aged 3-24months received either an infant formula supplemented with the live bacteria at concentrations similar to those previously shown to have clinical benefits, for periods of up to 1 year, or a probiotic free infant formula. The probiotic-supplemented formula was well tolerated and resulted in adequate growth. There was a significantly lower reported frequency of colic or irritability and antibiotic use, and infants who received the probiotic supplemented formula tended to have a less frequent need for health care support.

♦ Atopic disease and atopic dermatitis

Recent literature indicates that changes in gut microflora induced by the consumption of probiotics may be associated with the frequency and severity of atopic disease in infants. In a recent clinical trial, Lactobacillus rhamnosus GG was reported to be effective in the prevention of early atopic disease in high-risk children. This probiotic strain was given prenatally to mothers with a family history of atopy and postnatally to their infants for 6 months. Compared with the placebo, the probiotic significantly reduced the incidence of atopic eczema during the 2-year follow-up period. The combination of Lactobacillus rhamnosus 19070-2 and Lactobacillus reuteri has also been reported to have a therapeutic effect in the management of atopic dermatitis in children. The emerging relationship between probiotics and atopic disease is indeed promising, but the exact role of probiotics in atopic disease in humans is not clear and must await further clarification before any recommendations can be made.

SAFETY

Fermented foods have been consumed safely by many generations and as such, on their own, they generally do not raise safety concerns. However, the type of microorganisms found in probiotics need to be very carefully evaluated before they are marketed. Certainly, the available evidence indicates that *Lactobacilli* and *Bifidobacteria* have a very low potential to cause disease

(pathogenicity) even in people with decreased immune function, and that these bacteria also form part of the spectrum of microorganisms normally found in the gut.

Endocarditis, pneumonia and meningitis have very rarely been reported in association with lactobacilli. Most of these isolated reports however, were in significantly immunocompromised individuals. Several cases of bacteraemia with *Saccharomyces boulardii* have been reported, which raises concern over the use of this yeast in immunosuppressed patients or patients with underlying disease. In this regard, the potential of microorganisms to cause disease, especially in individuals with underlying illness (es), should never be ignored. As with any new food ingredient, the safety of any new strain of microorganisms must be clearly established before being introduced into food products.

BENEFICIAL EFFECTS OF PREBIOTICS ON HEALTH

Inulin, oligofructose, lactulose, galactooligosaccharides and synthetic fructoseoligosaccharides (FOS) are probably the only prebiotics for which available scientific evidence would indicate limited and defined health benefits. The chemical structure of these prebiotics prevents their digestion in the small gut. Consequently, they reach the large bowel undigested and are fermented by bacteria. This fermentation stimulates the growth of *Bifidobacteria*, a species used in probiotics. The ability of these oligosaccharides to alter the gut microbial population towards a more beneficial composition has been consistently shown in human studies. The greatest benefit appears to be in those individuals with low levels of bifidobacteria. It must be pointed out that the daily intake of prebiotics can be increased by dietary means, which includes the regular consumption of leeks, artichokes, garlic, onions, wheat and wheat products, asparagus and bananas. The average daily intake of these prebiotics from food ranges from 1-4 g in the U.S.A. to 3-11 g in Europe. Although there is no daily recommendation for prebiotics, doses of 4-20g per day have shown efficacy. Many other potential prebiotics are currently under investigation, including xylooligosaccharides, lactitol, soyoligosaccharides, pecticoligosaccharides, glucooligosaccharides, isomaltooliosaccharides and gentiooligosaccharides.

Prebiotics have also been associated with a reduction in the risk for diarrhoea, constipation, colon cancer, osteoporosis and heart disease. Their effect in improving constipation is largely attributed to increasing faecal bulk and improving gut motility.

♦ Prebiotics in infant health and nutrition:

Studies have shown that the gut microflora of breast-fed infants is dominated by bifidobacteria; whereas the gut microflora of infants fed infant formula have a diverse composition (higher numbers of *Bacteroides* spp., *Clostridium* spp. and *Enterobacteriaceae*). The high proportion of *bifidobacteria* present in the gut of breast-fed infants is associated with lower risk of intestinal infection. There is evidence that human milk oligosaccharides may promote the proliferation of intestinal *bifidobacteria* and *lactobacilli*, thus contributing to the natural defences against infection. Since the composition and structure of human milk oligosaccharides cannot be entirely reproduced by the food industry, prebiotics are being considered for fortification of infant formulas. In South Africa, there are formulas fortified with prebiotics for the infants older than 6 months. Preliminary studies have reported that infants fed a cow's milk formula supplemented with fructoseoligosaccharides and galactooligosaccharides had a significantly increased number of faecal bifidobacteria after 28 days of feeding.

♦ Colorectal cancer (CRC)

Preliminary evidence indicates that inulin, fructoseoligosaccharides, lactulose and galactooligosaccharides appear to have a positive effect on biomarkers of CRC. These studies suggest that prebiotics may even have the potential to reduce the risk of CRC and alter its progression. The mechanism(s) underlying these effects are unknown and the association between prebiotics and CRC requires extensive additional investigation.

SAFETY

Concerns have been expressed that prebiotics may impair the absorption of minerals in the small gut by a binding and/or sequestering mechanism. The clinical importance of such an interaction,

however, has not been established. On the contrary, these prebiotics have been proposed to enhance the absorption of calcium and magnesium from the colon, an interaction that also needs to be better defined in clinical terms. For instance, a significant increase in calcium absorption has been observed in adolescent girls who were given a drink fortified with fructoseoligosaccharides and inulin (4g per day) and a daily supplement of 1 500 mg of calcium per day.

It is well accepted that one of the side effects of consuming large quantities of these prebiotics is associated with abdominal distention and discomfort as well as significant flatulence. These side effects were observed at prebiotic doses higher than 20g per day. Excessive consumption of such products is therefore not recommended.

RECOMMENDATIONS:

- The use of probiotic supplements should be considered in antibiotic treatment to prevent antibiotic associated diarrhoea and further complications, which have cost implications in patient care.
- Infants and young children in daycare centers, who are at greater risk for frequent gastrointestinal infections, might benefit from probiotic supplementation. The available supplemented follow-on milk formulas can be a convenient method to include probiotics in their diets. Bifidobacterium bifidum, given in conjunction with Streptococcus thermophilus in standard milk formula, has been shown to reduce the incidence of rotaviral diarrhoea.
- Fermented dairy products are a convenient, culturally acceptable and safe method to increase probiotic intake. These products are also excellent sources of other nutrients such as calcium and protein.
- Good dietary sources of prebiotics include leeks, artichokes, garlic, onions, wheat and wheat products, asparagus and bananas. Prebiotics supplements, if necessary, should not be consumed in excess of the recommended amounts because of their known and unpleasant side effects

CONCLUSION

Although many studies have contributed greatly to our understanding of the role, real and potential, of gastrointestinal microflora in health and disease, we are still lacking a comprehensive understanding of the strength of the reported associations in relation to long-term clinical outcomes as well as to the degree of variation within and among individuals. It is clear however, that the modulation of gut microflora has the potential to improve human health and possibly to reduce the onset of disease. Certainly, nutrition and food technology will continue to make great strides in the better understanding of the important role of food in our health and well-being. In the process, the benefits, which can be derived from various foods, as granny taught us, will be explored to the full. **No single food item on its own, however, has so far been shown to be, neither is it likely to be shown to be in the future, the "magic bullet" for good health.** The latter can only be achieved by correct nutrition, which can simplistically be summarized as eating a variety of foods and maintaining an appropriate body weight for the age and gender of an individual.

For further, personalized and more detailed information, please contact NICUS or a dietitian registered with the Health Professions Council of South Africa (previously known as the South African Medical and Dental Council).

References from the scientific literature used to compile this document are available on request.

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