Probiotics: "conbiotics" or medicine of the 21st century?

Probiotics are the subject of continued and intense investigation. Recommendations in the lay media for the use of probiotics are multiple and, more often than not, not evidence based. For many years, the advantages of probiotics such as bifidobacteria and *Lactobasillus acidophilus* have been stated on the labels of fermented dairy products. This was, however, more anecdotal than based on sound research. The fact that, in 2010, more than 28% of the 5 466 publications on this topic on Pubmed were reviews, supports the opinion that insufficient original research is being conducted.[1]

The assumed benefits of the consumption of probiotic-containing functional foods were, and still are, promoted extensively. However, the long-term consequences of this practice have not been studied in children. In addition, it is worth considering that certain strains of probiotics are used as growth promoters in animals, increasing the size and weight of young animals. Do we know if this happens in humans? Could we be, unwittingly, promoting the worldwide obesity epidemic?[2] Consider the following: probiotics have been shown to influence the immune response and obesity in inflammatory conditions.[3] Evidence also suggests that the gut microbiota is involved in the extraction of energy from food and assists with the storage of energy in adipose tissue,[4] and that probiotics can modulate gut peptide YY and glucagon-like peptide-1 secretion.[5] Suddenly, Raoult's suggestion about a link between probiotics and obesity[2] not only makes sense, but also causes some concern.

On the other hand, some interesting data on the benefits of probiotics are emerging. For instance, *L. rhamnosus* GG has been effective in paediatric obesity-related liver disease, but the results of this study need to be confirmed in a larger population.[6] Martarelli et al suggest a possible mechanism for decreased infections in athletes, with the use of probiotics.[7] Although the study was, again, small, the authors were able to show that a combination of *L. rhamnosus* IMC 501® and *L. paracasei* IMC 502® increased antioxidant levels and reduced physical activity-induced oxidative stress. The same combination also improved bowel habits in adults.[8] Minimal hepatic encephalopathy is a devastating consequence of liver cirrhosis. The reported significantly beneficial effect of probiotics may, on occasion, be the only option for improvement of the quality of life of these patients.[9]

Strong commercial interest has been suggested to be primarily responsible for the worldwide escalation in probiotic use.[10] It may be that, like other folk remedies,[10] probiotics may have little, if any, real medicinal value. On the basis of a few well-controlled studies and the fact that the suggested mechanisms of action remain to be confirmed, the term "conbiotics" has been coined.[10]

Undoubtedly, the appropriate perspective on the medicinal value of probiotcs must lie somewhere between these two extremes, the claims of the lay media and those who use the term "conbiotics".[10] In this regard, the title of a recent article, "Probiotics: guidelines, science and human studies catch up with folklore" may be a reasonable summary of our current knowledge.[11] To date, the available evidence indicates some benefit I the use of certain microbial strains, in defined populations and clinical settings. For example, *L. rhamnosus* GG (ATCC 53013) has been shown to be effective in rotavirus diarrhoea in children and infants, an effect that has been documented in different populations and verified by the European Society of Paediatric Gastroenterology and Nutrition.[12] Both the mechanism and clinical effects have also been validated by various research groups.[13] It should, however, be borne in mind that, because probiotics are strain specific, other strains within *L rhamnosus* or other species within the *L actobacillus* genus may not be effective in this setting.

The review by Stevenson and Blaauw in this issue of the *SAJCN* highlights not only the importance of strain-specific treatment, but also adequate subgroup definition in a setting of disease heterogeneity, such as the irritable bowel syndome. Furthermore, there is also good evidence for the use of a functional food product, like yoghurt, containing a specific probiotic *(Bifidobacterium animalis* DN173010) which has been reported to significantly improve colonic transit time,[14] and which may be helpful in the management of constipation. It has also been shown that that VSL#3 can maintain remission in about 85% of patients treated for pouchitis.[15,16] On the other hand, most studies on the use of probiotics for the eradication of *Helicobacter pylori* have so far been disappointing, although improved treatment tolerance to triple therapy has been reported.[17, 18] A recent in vitro study has also documented that a very specific strain of *Bifidobacterium, B. bifidum* CET 7366, is able to inhibit *H. pylori* (close to 95% inhibition level) under certain conditions,[19] a finding that remains to be confirmed in humans. Furthermore, the mechanism of this effect must be explored.

In the light of the benefits probiotics are reputed to have and, in specific instances, do have, there is a need for investigation of the potential or real harms that can be caused by probiotics. These are often insufficiently appreciated or understood. Why, for instance, after administration of a combination of lactobacilli and bifidobacteria, was the mortality doubled in a group of patients with predicted severe acute pancreatitis (SAP)?[20] On the

other hand, why did *L. fermentum* VRI-003 halve the frequency of respiratory infections in long-distance athletes?[21] Have the questions been asked: What probiotics should one use? Should a single probiotic or a cocktail of probiotics be given? When, and how, and for how long should probiotics be administered? In the SAP patients in whom mortality was increased, a large dose of the probiotic was administered in the small intestine, which is prone to bacterial overgrowth, with a large dose of fibre, for good measure. Which factor or combination of factors caused the higher mortality, particularly since studies using a single-strain probiotic showed a benefit in pancreatitis? [22,23] Admittedly, the SAP patients were critically ill, a very different scenario from a healthy person consuming a yoghurt for breakfast. Yet, a very high dose of probiotics, mixed with fibre, was administered in the jejunum. Not the usual way to consume probiotics. Did bypassing the stomach or the altered gut permeability of critically ill patients contributed to the higher mortality? Such questions need to be asked, and answered, if probiotics are ever going to be used immunopharmacoligically.

Clearly, there are many gaps in probiotic research, which fuels the prevailing confusion and results, on occasion, in detrimental and unacceptable outcomes. The International Life Sciences Institute has identified the following targets to improve research outcomes in probiotic research: the investigation of efficacy of probiotics should be directly tested on the target population, and the target population must be clearly defined; the protocol design must allow for the correlation of surrogate end points with clinical end points; the background diet must be standardized; a product effect must be determined; and proper strain identification must take place.[1]

The consensus statement from the workshop, entitled *Probiotics and Health: Scientific Evidence,* [24] also stresses that the health benefit of probiotics must be investigated in the intended population of use. Thus, laboratory or animal studies, although necessary for particularly identifying mechanisms of action, must be repeated in a human population before any claims can be made. In addition, evidence for the use of a specific probiotic, tested in a specific target group, cannot be extrapolated to other groups of a different age or physiological state.[24]

Stevenson and Blaauw eloquently discuss the limitations of probiotic research outlined in this editorial. For instance, study groups are not divided into subgroups, nor are subgroup analyses performed. The role of indigenous microbiota is also not considered. Indeed, meta-analyses need to be assessed with caution. Because the effects of probiotics are strain specific, pooling data relevant to different probiotics, different conditions and different patient characteristics may result in the identification of a non-effect,[1] or the manifestation of adverse (and fatal) events, as the SAP trial clearly demonstrated.[20] Often, the background diet is not reported or not taken in consideration, and this may result in a bias towards the claimed effects of the probiotics. These dietary components need to be standardised in both the control and treatment groups, e.g. saturated fat intake, which may have an independent effect on cholesterol, in trials evaluating the effects of probiotics on blood lipids. Often, the food matrix composition or general processing of a food may play a role in the efficacy of a probiotic.[1] For instance, the question has been asked[10] whether the benefit of eating fermented products lies in the probiotics per se, or in the fermentation products such as lactic acid, or in the antagonistic effect of lactic acid bacteria on the pathogens that grow in milk.

Unless studies are designed, while keeping the guidelines suggested in mind, we may never be able to elucidate mechanisms of action and interactions. There will, then, always be a risk of variable and inconclusive research outcomes, which will continue to be of little clinical value.

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