BIG NEWS: Probiotics could lower cholesterol?

Nah Li Ching
Executive Editor

Results of a recent study suggested the potential indication of a probiotic as an adjunctive therapy for the treatment of hypercholesterolemia. Published online in the September 2012 issue of the European Journal of Clinical Nutrition, hypercholesterolemic subjects who consumed *Lactobacillus reuteri* NCIMB 30242 capsules had reduced LDL-C levels after 9 weeks of treatment in a randomized controlled trial[4].

A total of 127 subjects completed the randomized, double-blind, placebo-controlled, parallel-arm, multicenter study. Otherwise healthy hypercholesterolemic subjects between 20 and 75 years (inclusive) with LDL-cholesterol (LDL-C) >3.4 mmol/l, triglycerides (TGs) <4.0 mmol/l, body mass index of 22-32 kg/m^2, not receiving or receiving a stable dose of statin monotherapy (≥3 months) and at least 80% compliant with product consumption were included. They were randomized to consume *L. reuteri* NCIMB 30242 (≥2.0 x 10^9 CFU per capsule) or placebo capsules twice daily at breakfast and dinner over a 9-week intervention period. The primary outcome was LDL-C relative to placebo at the study end-point.

Results show that *L. reuteri* NCIMB 30242 capsules attained significant reductions in LDL-C of 11.64% (P <0.001), total cholesterol (TC) of 9.14% (P <0.001), non-HDL-C of 11.30% (P <0.001) and apoB-100 of 8.41% (P = 0.002) relative to placebo at the study end-point. The ratios of LDL-C/HDL-C and apoB-100/apoA-1 were reduced by 13.39% (P = 0.006) and 9.00% (P = 0.026), respectively, relative to placebo. TGs and HDL-C were unchanged. High sensitivity C-reactive protein (hs-CRP) and fibrinogen were reduced by 1.05 mg/l (P = 0.005) and 14.25% (P = 0.004) relative to placebo, respectively. Mean plasma deconjugated bile acids were increased by 1.00 µmol/l (P = 0.025) relative to placebo, whereas plasma campesterol, sitosterol and stigmasterol were decreased by 41.5%, 34.2% and 40.7%, respectively.

Many preclinical evidence have pointed out that an increase in the bile salt hydrolase (BSH) activity of the intestinal microflora increases the deconjugated bile-acid pool, which in turn lead to increased hepatic cholesterol catabolism and reduced cholesterol absorption. Germ-free animals were reported to accumulate more cholesterol than their conventionally raised counterparts, and in the absence of gut microbiota, biliary bile acids and cholesterol absorption are increased by 300% and 25%, respectively. Follow-up studies confirmed that germ-free animals have elevated conjugated bile acids throughout the intestine with no deconjugation and significantly decreased faecal excretion. It has been hypothesized that increases in deconjugated bile acids may result in reduced farnesoid X receptor activation, increased cholesterol catabolism, reduced inhibition of liver X receptor (LXR) and upregulation of adenosine triphosphate-binding cassette (ABC)G5/G8 transporters. These transporters efflux cholesterol from hepatocytes and enterocytes and are stimulated in the presence of deconjugated bile acids.

The study findings indicate that increased intraluminal BSH activity, in response to *L. reuteri* NCIMB 30242 supplementation, leads to an increase in deconjugated bile acids, a reduction in non-cholesterol sterol absorption and serum cholesterol, which is consistent with much of these hypotheses. The ability of *L. reuteri* NCIMB 30242 to decrease LDL-C, LDL-C, TC, apoB-100, non-HDL-C, fibrinogen and hs-CRP - all considered to be cardiovascular risk factors - was seen at the 9-week end point. Increased plasma deconjugated bile acids and reduced plasma non-cholesterol sterols campesterol, sitosterol and stigmasterol suggest an effect on the absorption of these compounds and a novel cholesterol-reducing mechanism of action. These results show that *L. reuteri* NCIMB 30242 can be used to reduce serum LDL-C, likely by its effect on cholesterol absorption, and indicate its potential as an adjunctive therapy for the treatment of hypercholesterolemia.

Quick Facts

Because health benefits of probiotics may be strain-specific, providing the genus, species, and strain for each probiotic organism is imperative in clinical publications as well as on product labels[5].

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Message from the Editor

Over the last fifty years, numerous research into the different clinical applications of probiotics have been studied.

We highlight one particular new probiotic, which can be used as an **adjunct therapy for the treatment of hypercholesterolemia** in this issue.

That, together with renowned Prof Seow-Choen's article on **Probiotics and Colonoscopy** will hopefully satisfy your reading palate.

We take this opportunity to wish our Muslim readers "Selamat Hari Raya Adifitri" as well.

God Bless!

Melvin Wong
Editor-in-chief

Probiotics and Colonoscopy

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Introduction

The human colon is jammed packed with micro-organisms. There are about 100 trillion micro-organisms in the human intestines. This is more than ten times greater than the total number of cells in the human body. Microbiologists have also estimated the number of species of micro-organisms in the gut to be around 500. However, about 99% of the actual micro-organisms present probably come from 30 to 40 species only. Bacteria can make up from 40 to 75% of the dry weight of faeces. The primary benefit of these organisms to the host is the production of energy for the bacterial fermentation of undigestible carbohydrates and short chain fatty acids. Some of the most important metabolites are butyrates used by the colonic cells, propionates used by the liver cells and acetates for the muscle cells. Gut bacteria also produce Vitamins B and K as well as metabolizing bile acids. Gut bacteria also help in the normal development of the immune system and prevent the growth of harmful pathogenic bacteria.

Most gut bacteria therefore live in a peaceful co-existence with the human hosts. Occasionally however, there can be pathogenic infiltration of the human tissues leading to infection and disease.

Probiotics however, are micro-organisms that may be beneficial to humans; although actual proof may be insufficient from a purely scientific point of view at this present time. Suitable micro-organisms must be capable of producing antagonistic metabolites against dominating pathogenic micro-organism and be proven to not cause ill effects. Nonetheless, probiotics are in wide clinical use at this current time.

Colonoscopy and probiotics

Colonoscopy on the hand is a common procedure that is often performed both for diagnostic as well as therapeutic purposes. The question is whether probiotics help in the performance of colonoscopy as well as whether colonoscopy interferes with normal colonic bacterial interaction is an interesting one.

For many years now even before the widespread use of probiotics, we have often noticed that following colonoscopy a proportion of patients had had spontaneous resolution of symptoms of irritable bowel syndrome including diarrhoea, abdominal bloating as well as cramps and pain. Some of these patients have had long term resolution of symptoms; others had short term resolution of such symptoms. On closer scrutiny of these patients, it was found that many but not all of these patients with complete or partial symptomatic resolution had had irritable bowel symptoms following a bout of gastroenteritis or following ingestion of a course of antibiotics. I postulated that the resolution was due to the eradication by the bowel preparation which washed out the symptom causing micro-organisms. Relapse was probably related to re-introduction of the micro-organism or related micro-organisms.

The widespread availability of commercially prepared medical grade probiotics had enabled this hypothesis to be further tested in the clinic. Patients with irritable bowel or irritable bowel-like symptoms now have a course of probiotics following colonoscopy in my practice as a routine. After such a course, I have found symptom resolution to be much improved compared to when probiotics were not used. This had re-enforced my ideas that the wash-out of disease causing micro-organisms and their replacement by beneficial micro-organisms may cure irritable bowel or irritable bowel-like syndromes. This of course has still to be formally tested in a clinical trial.

Nonetheless, other researchers had looked at the feasibility of using probiotic pretreatment as part of bowel preparation to improve colonoscopic visualization and found that gastrointestinal symptoms were also reduced as a result[1]. In this particular study, the clinicians from Seoul Korea prospectively randomized patients to receive either a 2 week course of probiotics or placebo in two groups of patients with and without constipation. They found that pretreatment with probiotics improved bowel preparation in constipated patients and that post-colonoscopic gastrointestinal symptoms were also reduced.

Conclusion

The scientific evidence currently is weak for the routine use of probiotics peri-colonoscopically. However, my own clinic observations are such that probiotics are very useful in the dramatic reduction of irritable and irritable bowel-like symptoms. I recommend that further prospective randomized research be done in this area to clarify its use, efficacy as well as the possibility of side effects. In the meantime, my own anecdotal evidence pushes me to continue to use and observe the usefulness of probiotics on the patients well-being following colonoscopy for patients with irritable bowel and irritable bowel-like symptoms.

Mono- vs Multi-strain Probiotics

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A probiotic product is a strain-specific preparation targeting different human metabolic functions to improve health by either supporting host physiologic activity or by reducing the risk of disease. It has been generally accepted that the probiotic potential of different strains of the same species may have different probiotic effects.

Mono-strain probiotics

Mono-strain probiotics are defined as probiotics containing one strain of a probiotic species[2]. Different species of lactic acid bacteria produce many metabolites with documented antimicrobial effects such as lactic, acetic, and succinic acids. In addition to species differences, major strain-specific differences also exist. Some strains may additionally produce butyric acid, hydrogen peroxide, and bacteriocins that act as functional tools that could be applied in humans. Mikelsaar and co-workers have listed some potentially new biomarkers produced by *L. fermentum* ME-3, including glutathione peroxidase, reductase, NO and polyamines.

Multi-strain probiotics

Multi-strain probiotics contain more than one strain of the same species or closely related species[2]. It also refers to multi-species probiotics that contain strains of different probiotic species that belong to one or more genera. On one hand, there may be antagonistic relationships between combinations of strains, if some strains of the probiotic preparation include *Lactobacillus* spp. that include subclass IIb plantaricin genes that suppress the growth of other species of lactobacilli. On the other hand, preliminary results demonstrate that some combinations of different bacterial species, due to increased concentrations of quorum-sensing molecules, exhibit an increased probiotic potential, resulting in interference with pathogen growth and expression of virulence and antibiotic resistance markers in a synergistic manner.

Assessment of efficacy of mono- or multi-strain probiotics

Under ideal conditions, different mono- or multi-strain probiotics should be characterized using strain or combination-specific metabolic properties[2]. In the prevention of disease or during supportive treatment of various disorders and improvement of metabolic stress, the rationale for the choice of a particular mono-strain probiotic or multi-strain probiotic combination should be described in peer-reviewed clinical trial studies. Unfortunately, there are no regulatory requirements defining the optimal number of viable organisms in a probiotic product required for use or the daily dose that is necessary for the achievement of documented evidence-based health effects for specific diseases.

Multi-strain or multi-species preparations may have advantages when compared to mono-strain probiotics since they can benefit from a certain amount of synergism when different probiotic effects of different probiotic strains or species are combined. In a review article by Timmerman and his fellow researchers[3], they concluded that multi-strain and multi-species probiotics are superior to mono-strain probiotics in treating antibiotic-associated diarrhoea in children, and protecting animals against infection with *Salmonella Typhimurium*, *S. Enteritidis*, and *Escherichia coli*.

However, when two mono-strain *Bifidobacterium longum* (BB536) and *Lactobacillus johnsonii* (La1) probiotics in a mixture were perioperatively administered to colorectal cancer patients, the evaluated strains differed in their functional properties[2]. La1 and not BB536 adhered to colonic mucosa and affected the intestinal pathogens. These results suggested that a more strict evaluation of the role of single components of multi-strain probiotic need to be performed depending on the application for which it is intended.

To date, there are several probiotic products composed of multiple species of lactobacilli with diverse functional properties that are documented by *in vitro* and animal experiments that when used during clinical trials may meet the standards for health claims acceptable for EEFA (Regulation No. 1924/2004). There are also several examples of concordance between the metabolic properties of a single probiotic strain and the specific effects on human health[2].

Comparison of effects of mono- versus multi-strain probiotics

Probiotics have been documented to have activity in treating a variety of clinical conditions - ranging from infantile diarrhoea, necrotizing enterocolitis, antibiotic-associated diarrhoea, relapsing *Clostridium difficile* colitis, *Helicobacter pylori* infections, inflammatory bowel disease, female urogenital infections, and surgical infections.

In a meta-analysis of 25 double-blind placebo-controlled trials comparing the efficacy of mono- versus multi-strain probiotics in the treatment or prevention of different diseases including infectious diarrhoea, antibiotic-associated diarrhoea and *Clostridium difficile* infection, *Helicobacter pylori* infection, IBS, IBD and pouchitis, it was found that the mono-strain probiotic preparations (17 trials) were effective in 41% of cases, whereas the multi-strain ones (8 trials) expressed somewhat higher (63%) efficacy. In IBS (16 trials), the total efficacy was 75% while by applying mono-strain preparations, the efficacy was 67% and multi-strain probiotic preparations 86%. In 18 trials with patients with IBD, the high preference for multi-strain probiotic efficacy (40% vs. 100%) was registered[2]. The reasons for better efficacy of multi-strain probiotic preparations seemingly derive from the large individual interrelations between microbiota and health markers of humans apparent also in case of GI diseases.

Conclusion

Probiotic strains of specific species, either in mono- or multi-culture, should have specific and well-defined metabolic and functional properties measurable by objective criteria. The probiotic effect should target a particular host function that has been altered through environmental stress, antibiotic utilization, or during specific clinical diseases that result in the alteration of the normal microbiota.