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Review Article

Microbiology Section

Probiotics and their Effects on Metabolic Diseases: An Update

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ABSTRACT

Probiotics are lactic acid bacteria which are used extensively in therapeutic preparations and added to foods. There are many studies which have demonstrated the effects of probiotics on metabolic diseases. One study has shown the effect of fermented dairy products on the serum cholesterol, especially with selected strains of lactic acid bacteria. It has been found that a minute quantity of the dry culture of *Lactobacillus fermentum* KC4b, for example, can remove 14.8 mg of cholesterol from the culture medium. Lactobacilli also play an important role in deconjugating the bile salts in the intestine to form bile acids and thereby inhibiting the micelle formation. Probiotics reduce the lipid peroxidation and improve the lipid metabolism in vivo. The addition of probiotics to the diet for weeks improved the immune response without the release of inflammatory cytokines, thereby reducing the onset of systemic inflammatory induced diabetes. There are evidences that the differences in the composition of the gut microbiota may precede the development of obesity in children. This review has illustrated the potential of probiotics in mediating metabolic diseases via the positive modulation of several different physiological systems, apart from its conventional benefits for the gastrointestinal health.

Key Words: Probiotics, Metabolic diseases, Hyperlipidaemia, Lactobacillus, Diabetes, Obesity

INTRODUCTION

In the early 20th century, a Russian scientist and Nobel laureate, Metchnikoff introduced the notion of advantageous bacteria. He mentioned in his book, "The Prolongation of Life", that one should absorb large quantities of advantageous bacteria, as they have many health benefits to confer to the host. He suggested that there was a potentiality for the modification of the gut micro flora and the replacement of harmful microbes by beneficial bacteria i.e. probiotics [1]. The safe use of probiotics has to be studied well, before introducing them into humans, as was suggested by Ishibashi et al., and Eaton [2,3]. The probiotics are generally consumed as a part of the fermented foods with specially added active live cultures; such as in yogurt and soy yogurt, or as dietary supplements. The Joint Food and Culture Organization (FAO) and the World Health Organization (WHO) Working group described that probiotics must have live microorganisms and that they should confer a measured physiological benefit [4]. In accordance to the FAO and the WHO guidelines, probiotic organisms which are used in the food must have the ability to stay alive in the gastric juices and they should be resistant to the exposure to the bile in the human gut. In addition, they must have the ability to flourish and colonize the digestive tract of humans. On top of these features, they must be safe and effective and they must sustain their efficiency for the entire period of the shelf-life of the product. According to Hikey, as we begin to appreciate the practical significance of microbes on the human physiology and disease, new therapeutic perceptions have emerged to provide novel approaches in the treatment of both acute and chronic diseases [5]. Presently, the area of probiotics lies in between food and medicine, but this difference will reduce, as we have advanced into the genetic modifications of the advantageous bacterial species for drugs and nutrient production in the human gut. Characteristically, probiotics are LAB (lactic acid bacteria), which are used extensively in therapeutic preparations and are added to foods. At present, specific health outcomes are being investigated and documented, which include the alleviation of chronic intestinal inflammatory diseases as was stated by Mach, the prevention and the treatment of pathogen-induced diarrhoea as was observed by Yan et al., urogenital infections as were studied by Reid and atopic diseases as were shown by Vanderhoff [6-9]. In addition, Gilliland found out that the benefits of the regular consumption of probiotics included the reduction of the risk of colon cancer, the cholesterol levels, the incidence of diarrhoea and the stimulative effects on the immune system [10]. All the effects which are observed can only be attributed to the individual strain(s) which are tested i.e. the testing of a supplement does not indicate a benefit from any other strain of the same species. The most promising probiotic strains include the members of the Genera-lactobacillus, bifidobacterium, and enterococcus. The representative species as has been stated by Fuller and Gordin, include *Lactobacillus Acidophilus, L. johnsonii, L. casei, L. gasseri, L. plantarum, L. rhamnosus; Bifidobacterium longum, Bifidobacterium breve, Bifidobacterium bifidum, Bifidobacterium infantis; Enterococcus faecalis* and *Enterococcus faecium*. Even though, the health benefits of probiotics are generally acknowledged by scientists, doctors and consumers, however, the underlying molecular mechanism still remains controversial [11].

HYPERLIPIDAEMIA

Murray et al., documented that hyperlipidaemia and atherosclerosis are the leading causes of the cardiac illnesses and the mortality in the world. It was demonstrated by McGill, that there exists an association between the serum cholesterol levels and the risk for coronary Heart Disease (HD) [12].Globally,hyperlipidaemia causes almost double the number of deaths as those which are caused by cancer and 10 times as those which are caused by ac-

cidents. After Mann et al., reported a hypocholesterolaemic effect in the Maasai tribesmen which was due to the fermented milk of the wild type starters, several studies have been performed in experimental animals and humans. St. Onge et al., demonstrated the effect of fermented dairy products on the serum cholesterol, especially with selected strains of lactic acid bacteria, by increasing the utilization of cholesterol for the de novo synthesis of the bile acids [13].

During the lipid metabolism, micelles formation occurs, which aids in the absorption of cholesterol in the intestine. Emulsification of the dietary fat is an intermediate step in the absorption of fat. Lactobacilli play a role by deconjugating the bile salts in the intestine to form bile acids, thereby inhibiting the micelle formation. This leads to a decrease in the absorption of cholesterol. The cholesterol that enters the intestine through the enterohepatic circulation is treated similarly. The enzyme, Conjugate Bile acid Hydrolase (CBH) which is elaborated by Lactobacilli, hydrolyses the bile salts and the Hydroxyl Steroid Dehydrogenase (HSDH) and thus, degrades the bile salts and finally interrupts the enterohepatic circulation of the bile acids. Another factor which is thought to be elaborated by lactobacilli is the inhibition of hydroxy methyl glutarate CoA (HMG CoA). An elevated serum cholesterol level can be strongly correlated with coronary heart disease. Rao et al., demonstrated that in preclinical studies,feeding laboratory rats with fermented milk which was mixed with animal feed showed lower serum cholesterol levels in comparison to the rats which were fed with skim milk-supplemented feed [14]. This difference could not simply be a feature of the redistribution of cholesterol between the plasma, liver and the other body pools. Orotic acid, lactose, casein, and hydroxymethyl glutaric acid have been suggested to have the factors for hypocholesterolaemia. A placebo-controlled experiment evaluated the effects of probiotics fermented food on the serum cholesterol level in 20 mice. The experimental group was fed a food mixture which contained probiotics and 1% cholesterol, while the control group was fed only the latter for 42 days. It was reported that *L. casei* NCDC-19 (109 CFU*) and Saccharomyces boulardii (10 9 CFU) caused a 19 % decrease in the total serum cholesterol, whereas the LDL-cholesterol levels had decreased by 37%. Another study which was conducted as a placebo-controlled study on hypercholesterolaemia-induced pigs (Yorkshire barrows), found that the probiotic fed group had 11.8% reduced total blood cholesterol [15] . In a study, it was demonstrated that 36 male sprague-dawley hypercholesterolaemic rats had 25% reduced serum cholesterol and significantly reduced VLDL, IDL and LDL in comparison to the controls, after receiving a supplementation of L. acidophilus ATCC 43121 (2 × 106 CFU/day) [16]. In other study which was conducted by Yong Zhang et al., to observe the antioxidative effects of *Lactobacillus casei* on hyperlipidaemic rats, it was shown that the supplementation of *L. casei* significantly reduced the Malondialdehyde (MDA) levels, whereas the Superoxide Dismutase (SOD) and the glutathione peroxidase levels were increased both in the serum and the liver of these rats [17]. Thus, we can conclude that probiotics reduce the lipid peroxidation and improve the lipid metabolism in vivo.

Pereira et al observed in a study which was done on the in vitro cholesterol reduction abilities of probiotics, that the L. fermentum KC5b strain was able to maintain viability for two hours at pH 2 in bile acids and it was also able to remove a maximum of 14.8 mg of cholesterol per gram (dry weight) of cells from the culture medium [18]. Hence, it was regarded as a noble probiotic. In a controlled study, it was reported that fermented milk which contained L.acidophilus L1 reduced the serum cholesterol concentration by 2.4% ($p<0.05$) in the first treatment period [19]. Varied results have been shown by the human trials which were carried out on dairy foods which were fermented with specific lactic acid bacteria, which emphasized that the bacteria could produce modest reductions in the total and the LDL cholesterol levels. Nevertheless, the studies have suggested that probiotics can be a suitable approach to begin the therapy. Genetically modified soy milk with or without a probiotic fermentation can improve the hypercholesterolaemia and reduce the risk of atherosclerosis, as was shown in 112 male Golden Syrian Hamsters [20].

(* CFU- Colony Forming Units).

DIABETES

Arauz et al., observed that the incidence of hypertension in diabetic patients was 1.5 to 3 times more as compared to that in non-diabetics [21]. In a study, it was observed that the development of type II diabetes was almost 2.5 times more likely in those with hypertension than in normotensive individuals [22].

Irving et al confirmed the association between insulin resistance, high blood pressure and fasting hyperglycaemia [23].Furthermore, it was found that high blood pressure and fasting hyperglycaemia, in combination, alter the dermal microvascular structure. In another study, it was observed that the administration of dahi (an Indian fermented product) which contained *Lactobacillus acidophilus, L. casei* and *L. lactis* to fructose induced diabetic rats decreased the accumulation of glycogen in the liver of the rats [24].

Also,it was found that untreated,essential, hypertensive patients had higher fasting and post-prandial insulin levels than normotensive individuals [25]. The need of the hour is to assess the novel approaches to find out efficient methods for preventing or reducing the incidences of diabetes and hypertension with minimal side effects. In spite of the dearth of the anti-hypertensive drugs which are available in the market and the strong evidence about the benefit of the blood pressure control, nearly 75% of the diabetic patients do not achieve a good blood pressure control [26]. Therefore, the individuals who have essential hypertension are at a higher risk to develop diabetes. A new strategy that can be employed in the prevention or delay of diabetes and the subsequent reduction in the incidence of hypertension could be the consumption of probiotics. There are several studies which suggest that individuals who have consumed a high fat diet over long periods have a poor inflammatory status which is related with the onset of diabetes in such people. An inverse correlation was found between the population of the Bifidobacterium spp. and the concentration of lipopolysaccharides in plasma. It has been reported that in high-fat diet-induced diabetes, the concentration of the Bifidobacterium spp. in the gut was positively correlated with an improved glucose tolerance and glucose-induced insulin-secretion, as well as decreased diabetes endotoxaemia, plasma and adipose tissue inflammatory cytokines. One study has also shown that Bifidobacteria can reduce the intestinal endotoxin levels and improve the mucosal barrier and thus reduce the systemic inflammation and subsequently reduce the incidence of diabetes [27]. Al-Salami et al., (2008) [28] demonstrated that the pre-treatment of diabetic and healthy Wistar rats (n=10) with probiotics (75 mg/kg body weight) before the administration

of a gliclazide suspension, resulted in an optimum control over hyperglycaemia, as well as, that it showed improved signs and symptoms in those diabetic animals. The authors reported a significant increase in the gliclazide uptake which was induced by probiotics. There are 2 reasons which have been mentioned for this; firstly, the probiotic treatment can restore the activity of the drug transporters and secondly, restoration of the disturbed gut motility which is associated with diabetes. Such findings point towards the beneficial effects of probiotics in treating diabetes, in synergism with other diabetes drugs, thereby reducing the incidence of diabetes related hypertension.

It was demonstrated in a trial that the consumption of *Lactobacillus lactis* (1.5 x 1011 CFU) twice daily, by people who were in the age group of 60-83 years, for a period of 6 weeks, improved the immune response without the release of inflammatory cytokines, thus reducing the onset of systemic inflammatory induced diabetes [29]. The incorporation of the Ay gene into KK mice produced insulin resistant models. The dysfunction of the pancreatic β-cells causes a decrease in the insulin sensitivity in the regulation of blood glucose and fat metabolism, as was observed by Boden [30]. Matsuzaki et al., reported that the administration of a diet which was incorporated with lyophilized *Lactobacillus casei*, reduced the hyperglycaemia associated insulin deficiency [31]. Similarly, in another study, it was observed in 4-week-old, female, non-obese, insulin dependent, diabetic (nod) rats, which were fed with a diet which contained 0.05% lyophilized L.casei, the inhibition of the autoimmune destruction of the pancreatic β-cells was decreased [32]. The inactive ACE inhibitory peptides are present within the sequence of the parent protein, which can be released through fermentation by the microbial activity to form bioactive peptides. These peptides can be derived from a variety of fermented products like cheese, fermented milk, soymilk and yogurt.

Of the 70 identified enzymes, about 20 enzymes that are present at the highest levels in bovine milk, have been isolated from milk and they have been characterized [33]. The presence of a proteolytic system aids the probiotics to grow in milk products, as it degrades casein along with the lactose hydrolyzing enzymes, as was observed by Saito [34].

In another study, it was reported that the consumption of sour milk which contained 2.5-3.5 mg/kg/day of VAL-PRO-PRO and ILE-PRO-PRO, which was fermented by *L. helveticus* LBK-16H (10%), produced a reduction of 17 mm hg in the Systolic Blood Pressure (SBP), in Spontaneously Hypertensive Rats (SHR) [35]. In a human study, the intake of *Lactobacillus helveticus* and *Saccharomyces cerevisiae* by elderly hypertensive patients who were already on anti-hypertensive medication,showed a significant decrease in the Diastolic Blood Pressure (DBP) $p< 0.01$, after 8 weeks ingestion of sour milk, while the placebo group did not show any significant effect .In a study which was done on hypertensive subjects, it was observed that the consumption of 150 ml milk which was fermented by *L. helveticus* b.i.d., decreased the SBP and DBP by $p=0.001$ and $p=0.048$ respectively [36]. Yadav et al observed that probiotics are the potential modulators of the gut flora, that change the gut flora composition in a beneficial manner and exert various health effects .i.e. anti-oxidant, anti-inflammatory and anti hyperlipidaemic in type 2 diabetes mellitus patients [37]. Thus, the consumption of probiotics shields the impairment of the pancreatic β-cells, which plays a major role in the production of insulin molecules and thus, prevents the onset of insulin dependent diabetes as well as diabetes-related hypertension.

OBESITY

Obesity is one of the significant causes of avertable, adverse health conditions, morbidity and mortality, in addition to the use of health-care resources and its costs, as was observed by the US Department of Health and Human Services [38]. Ley et al., examined the faecal gut microbiota of 12 obese volunteers who had participated in a weight-loss program for a year. They were randomly assigned to either a fat restricted (FAT-R) or a carbohydrate-restricted (CARB-R), low-calorie diet [39]. The comparisons of each person's gut were made at the baseline and at 12, 26 and 52 weeks, which showed that, firstly, the obese subjects had a higher proportion of firmicutes and a lower proportion of bacteroidetes than the lean controls. Secondly, the subjects who lost weight had a reduced representation of the firmicutes and increased bacteroidetes, and thirdly, these changes were irrespective of the diet and they were in proportion to the amount of weight which was lost. Furthermore, it was observed that not just one member of the firmicutes or bacteroidetes respectively flourished or diminished, rather, it was a large group of microbes shifting up or down. As was shown in the preclinical studies, the members of the bacteroidetes and the firmicutes divisions dominated the microbiota, and the bacterial flora showed a remarkable intraindividual stability over time. It has been demonstrated in an animal study, that a high fat diet leads to increased levels of Lipopolysaccharides (LPS) in the serum [40]. Also, LPS, in conjunction with a high fat diet, enhances the symptoms of fatty liver. The cell walls of the gram negative bacteria consist of LPS which causes endotoxaemia, which in turn leads to an increase in the concentration of the proinflammatory cytokines in various tissues. On the other hand, a supplementation with oligofructose stimulates the bifidobacterial growth and it lowers the uptake of LPS from the gut lumen. This effect is also correlated with an improved glucose tolerance and insulin sensitivity.

In another study, Backhed et al suggested that the gut microbiota influences the energy harvest as well as the genes that regulate the energy expenditure and storage, i.e. both sides of the energy balance equation [41]. The distal gut microbiota of genetically obese mice and their lean littermates, as well as those of obese and human lean volunteers,revealed that obesity was associated with the changes in the relative abundance of the two dominant bacterial divisions, the bacteroidetes and the firmicutes. On the basis of these results, they indicated that the obese microbiome has an increased capacity to harvest energy from the diet. Furthermore, they colonized few germ-free mice with the obese microbiota and others with the lean microbiota, and found out that the obese microbiota produced significantly higher total body fat. This proved that the gut microbiota was an additional contributing factor to the pathophysiology of obesity [42]. In another study, Kalliomaki et al studied stool samples which were collected from children who were of 6 and 12 months of age and they were followed until they were 7 years of age, to analyze the gut microbiota composition. It was found that the children who were obese at the age of 7 years had fewer bacteroidetes then the leaner ones, whereas the obese children who were 6 and 12 months of age had more Staphylococcus aureus than the lean children [43]. This gave more evidence that the differences in the composition of the gut microbiota may precede the development of obesity. Lee et al., examined the

anti-obesity effect of *Lactobacillus rhamnosus* PL60 [44] in a study which was done on diet-induced obese mice. *L. Rhamnosus* is a human-derived bacterial species that produces conjugated linoleic acid, which was shown to reduce the body fat in animal studies. It was found that the obese mice which received *L. rhamnosus* had reductions in the body weight and the white adipose tissue (epididymal and perirenal), even though there were no changes in the energy intake [45]. In a recent, interesting, human study which was done on probiotic *Lactobacillus gasseri* (LG2055), it was demonstrated that there were significant reductions in the abdominal visceral and the subcutaneous fat areas, the body weight, the BMI, the waist and hip circumferences, and the body fat mass [46]. In a study which was conducted by Krishnan et al., to evaluate the effects of the probiotic, *L. rhamnosus* on the anthropometric parameters and the lipid profile in adults in comparison to sibutramine and atorvastatin, it was found that the subscapular skinfold thickness and the suprailiac skinfold thickness were significantly decreased at the end of a twelve weeks treatment [47]. These positive findings suggested the potential use of dietary alternatives i.e. probiotics, to alleviate the occurrence of metabolic diseases via a less radical approach as compared to drugs or a hormone therapy.

Versalovic suggested that with the expansion of the global efforts in the human microbiome-related research and the therapeutic microbiology, there was an increase in the understanding of the diversity and their functional consequences, present in the gastrointestinal tract but still extensive research work needs to be done in this area to reach any conclusion [48].

In a very recent study which was done by Murphy et al., in 2012, which involved mice which were fed on a low and a high fat diet along with vancomycin (dose 2mg/day), *L. salivarius* UCC118Bac+ and the bacteriocin negative derivative, *L. salivarius* UCC118Bac_ (each at a dose of 109 CFU/ day), it was observed that both the vancomycin and the bacteriocin producing probiotics altered the gut microbiota in the diet induced obese mice, but in different ways. The bacteriocin producing probiotic resulted in a relative increase in the bacteroidetes and the proteobacteria and a decrease in the actinobacteria as compared to the non- bacteriocin producing control [49].

According to Esposito et al., [50], the effects of the probiotic, VSL # 3 (a multistrain preparation which was composed of *Streptococcus thermophillus* and several species of *Lactobacillus* and *Bifidobacteria*) on young, male Sprague- Dawley rats, were anti- oxidative and anti- inflammatory. The liver TNF-α levels, the MMP-2 and the MMP-9 activities and expressions of iNOS and COX-2 were significantly reduced. The rats in this study were fed a High Fat Liquid Diet (HFD), which resulted in a greater body weight gain, fat mass and liver weight gain as compared to the rats which were fed a normal diet. Although, at the molecular level, the exact role of probiotics in the alteration of the lipid peroxidation, lipid metabolism and in the modulation of the physiological systems could be added, further studies are required to support these facts.

These results suggest the beneficial effects of probiotics on the metabolic disorders. Although researchers have been utilizing the science of genomics to make strides into the gut microbiota research, many more questions remain to be elucidated. Clearly, additional work is needed to better clarify the cause-and-effect relationship between obesity and the gut microbiota.

CONCLUSIONS

This review has illustrated the potential of probiotics in mediating metabolic diseases via a positive modulation of several different physiological systems, apart from their conventional benefits for the gastrointestinal health. Probiotics have exhibited their potential for the improvement of the lipid profiles, insulin resistance and glucose tolerance and the modulation of the ACE inhibitory peptides. These positive findings have suggested the potential use of dietary alternatives such as probiotics, to alleviate the occurrence of metabolic diseases with the help of a less radical approach, as compared to the drugs with milder known side effects. Probiotics could also serve as complementary supplements to enhance the well-being for those who are already suffering from diseases and taking drugs or hormonal therapy to medicate the condition. A further revelation on the potential of probiotics in future research could lead to a boost in the probiotic-fermented food industries–dairy and non–dairy. Nevertheless, more studies are needed to better understand the exact mechanisms, the in vivo target sites and the stability and safety, prior to using probiotics as an alternative treatment.

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