Opinion paper: *Lactobacillus* species causing obesity in humans; where is the evidence?

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Abstract
By definition, probiotics are to provide health benefits, and are expected not to cause any adverse effects in the general population. Recently, it has been suggested that probiotics, and in particular lactobacilli are contributing to human obesity. Here, we critically review the data available on this topic. The main misconception in this hypothesis is that growth in livestock and children equals with obesity in adults. The former two are expected to grow and probiotics may, by reducing disease risk, contribute to an improved growth. It is not correct to extrapolate this growth (of all tissues) to body weight gain (growth of adipose tissue) in adults. Furthermore, when looking at animal models of obesity, it even appears the lactobacilli may potentially contribute to a reduction in body weight. Epidemiological studies lend strength to this. We therefore conclude that there is no evidence that consumption of lactobacilli or probiotics in general would contribute to obesity in humans.

Keywords: *Lactobacillus acidophilus*, *Lactobacillus gasseri*, probiotics, obesity, overweight

Introduction

Probiotics are, by definition, considered to provide a health benefit to the consumer [WHO/FAO2002]. Being components of functional foods and dietary supplements, probiotics are expected not to have any side effects upon consumption by members of the general population. A few recent publications have suggested that consumption of probiotics (Raoult, 2009) and in particular certain *Lactobacillus* species (Million *et al*., 2012) is associated with human obesity also reduced faecal levels of *Bifidobacterium animalis* and *Methanobrevibacter smithii* have been suggested to be associated with obesity (Million *et al*., 2011). A food manufacturer's prime concern is the safety of the products it is producing; this is no different for probiotic products. As obesity is a serious health concern and thereby a food safety issue, the hypothesis that certain species of *Lactobacillus* would be contributing to obesity deserves to be investigated. Concerns on this hypothesis have earlier been published [Delzenne and Reid, 2009]. However, we feel that the latest publication (Million *et al*., 2012) in support for the hypothesis has a serious number of weaknesses that we feel need to be addressed.

Weight gain; livestock vs. human adults

In the report by Million and co-workers (2012) a meta-analysis is presented to determine if consumption of different *Lactobacillus* containing probiotics is associated with a species specific effect on body weight. Due to the limited availability of human data (3 studies included), the data was combined with observations from a larger number (30) of animal studies; predominantly farm animals.

By combining data from livestock and from infants to explain weight gain and obesity in fully-grown adult humans, Million and co-workers assume that growth at young age and obesity in adulthood are synonymous. However, while both involve body weight gain, the former is desirable and normal while the latter is undesirable. Probiotics are used in livestock to optimize the genetic potential for growth in young animals. The observed weight gain is a positive response to improved gut and immune health and less disease challenge and is typically manifested as lean muscle gain, not adipose tissue (Callaway and Ricke, 2012). Body composition of gained weight in livestock (lean vs. fat mass) is not considered in this meta-analysis, only the number on the scale. Equating muscle growth in young livestock and infants with obesity in humans is therefore incorrect. For similar reasons, have antibiotics been used in livestock as growth promoters; they counteract negative environmental challenges such as infections and allow the animal to grow closer to it's genetic maximum (Gustafson and Bowen, 1997). Although both antibiotics and probiotics are effective in promoting growth in young livestock by improving health and reducing the risk of diseases, the modes of action are different. Probiotics are used to enhance the healthy microbial homeostasis in the gut and the intestinal mucosa and have direct effects on host functions such as the immune system – thereby improving the host defenses against pathogens. Antibiotics, on the other hand, are active against a broad range of microbes and suppress both the pathogenic microbes as well as the healthy gut microbiota.

Weight gain; children vs. adults

The presumed *Lactobacillus*-caused obesity hypothesis, also equates growth in infants, which follows a similar pattern as growth in young production animals, with body weight gain and obesity in adulthood. In the case of *L. acidophilus*, the majority of the human data included in the meta-analysis (Million *et al*., 2012) comes from a single large infant study from the 1950's, which represent over 800 cases out of the 879 human subjects included in the analysis (Robinson and Thompson, 1952). In infants, good growth is desired (this would have been especially true for those post-WWII infants included in the study) and a reduced body weight would have been an undesirable outcome. Body weight gain in infants is not to be considered as “obesity”, as it relates to the normal growth of all the tissues in the body and normal increase in height. Probiotic-mediated improved growth in the post-WWII infants can easily be explained by reduced incidence of disease. Especially in children, probiotics seem to be able to reduce the risk for or duration of various diseases e.g. respiratory tract infections (Hao *et al*., 2011) and diarrhea (Salari *et al*., 2012). As with young production animals, it is very likely that reduced incidence and/or duration of disease is associated with improved growth; but not obesity. The authors of the meta-analysis themselves have given the *L. acidophilus* infant study the lowest quality score and estimated it to have high risk of bias. Despite this, the study has been included as a cornerstone in the analysis as it contributes 90% of the human data and a quarter of all of the included cases; the remaining three quarters are livestock.

Lactobacilli and body weight

In the case of the *L. acidophilus* review, of the included studies, only one study is potentially relevant to human adults, although the link with obesity is still missing; this is the study by de Roos and co-workers (1999) in healthy, non-obese adults. The authors of this study concluded that the differences in the weight gain in the probiotic group and placebo group were negligible; differences in means were 40g and 210g at two different time points. The direction of the differences was not disclosed as the weight changes between the groups were virtually equal and non-significant. A more relevant human study in overweight adults was performed by Andreasen and co-workers (2010); this study was not included in the review. In this study, no changes in weight were reported, but the consumption of *L. acidophilus* NCFM resulted in improved insulin sensitivity (which is often impaired in obesity).

The weight difference contributed to *L. acidophilus* is suggested by Million and co-workers (2012) to be 1½ kg for a 70 kg human. It is not clear whether this is weight gain per consumption of *L. acidophilus* or for the duration of the study; which in the case of production animals means a life time. Extrapolating the latter to humans (which is not appropriate) would mean a 1½ kg increase over your adult life. One can dispute the clinical relevance of that, particularly since the data presented by Million and co-workers (2012) suggest that the weight gain is related to growth at infancy and young age (nearly all data comes from young livestock or human infants).

It has been also suggested that lactobacilli probiotics may have a weight-reducing effect (Kootte *et al*., 2012). The data supporting the anti-obesity effect mainly comes from studies utilizing experimental animal models of obesity and diabetes. Unlike young livestock, these animal models are relevant for the study of obesity. The animals studied are adults, and their weight gain is obesity-related and often linked to the consumption of high-energy diets. In their meta-analysis, Million and co-workers (2012) also observed a weight reducing effect for, in particular *Lactobacillus gasseri*. The weight reduction quoted for *L. gasseri* is 6 kg for a 70 kg human; however, again it is unclear if this is per consumption or for life time consumption. Intriguingly, all included results contributing to the anti-obesity result of *L. gasseri* come from studies assessing probiotic effects in adult animal models and from a study with obese human adults. As with other lactobacilli, consideration of livestock data would change the conclusions. For example, a study by Baker *et al*. (2010) demonstrated that the presence of *L. gasseri* in the intestinal tract, contrary to the conclusions by Million *et al*. (2012), was associated with improved growth in weaning piglets. General conclusion from the data presented by Million and co-workers is that irrespective of the *Lactobacillus* species, the studies assessing the effect of lactobacilli in adult humans (overweight or obese) or in animal models of obesity suggest that probiotics either have no effect on weight or they reduce the weight and obesity. At the same time, studies in young livestock suggest a growth-promoting effect for probiotics. These conclusions are perfectly in alignment with each other, since growth in young livestock has nothing to do with obesity in humans, as discussed above.

In terms of timing, contrary to what has been suggested by Million *et al*., the increased prevalence of probiotics in food does not correlate with the increased prevalence of obesity. Obesity has been rising sharply from the 1970's, but the inclusion of probiotics in foods has really started to rise sharply in the 2000's – some 30 years after the beginning of the obesity phenomenon (Jankovic *et al*., 2010). Furthermore, probiotics have historically been included in foods first in Japan, followed by Europe and only recently in the US. Yet the rise in obesity has followed the opposite sequence, starting in the US, followed by Europe and only to a limited extent in Japan.

Lactobacilli in daily nutrition

From historical and evolutionary stand-point, the consumption of gram-positive bacteria (predominantly lactobacilli) in the human diet has reduced greatly with industrialization and modernization of the food processing and storage. In the pre-industrial age, the use of fermented foods – rich in lactobacilli- was much more prevalent than it is today. The bacterial load of food in the pre-industrial age has been estimated to be over 1000 times higher than they are today (Bengmark, 1998). Moreover, the during most part of human evolution, drying or burying food in caves and holes was the only method for preserving food, and these methods lead to natural fermentation of food – predominantly by lactobacilli. Probiotics offer a safe means for restoring the historically and evolutionary important balance between lactobacilli-containing diet and human health.

Epidemiological studies link consumption of lactobacilli with lower incidence of metabolic disorders including obesity. Consumption of yoghurt, high in lactobacilli, has been reported to be inversely associated with metabolic disorders (Beydoun *et al*., 2008) and with waist circumference, hypertension and metabolic syndrome (Azadbakht *et al*., 2005), and weight loss (Mozaffarian *et al*., 2012). While another study did not report significant correlations between yoghurt consumption and reduced body weight, it did detect beneficial effects on blood pressure (Snijder et al., 2007).

Conclusions

In all, we feel that there is no evidence that probiotics or lactobacilli are associated with human obesity. If anything, the data from the studies with obese humans or with experimental animal models of obesity suggest that certain *Lactobacillus* probiotics may actually be effective in reducing obesity. Intervention trials in adults would be welcome to test the effects of lactobacilli on human obesity. In fact, it is likely that several of the probiotic studies that have been performed in the past have registered body weight at the beginning and the end of the intervention. This data, that may not have been published as it was not considered relevant, should be revisited and may already in the short term provide an answer to the postulated obesity risk posed by consumption of certain *Lactobacillus* species. A recent epidemiological study published in the New England Journal of Medicine already gives a glimpse of the effects of lactobacilli on body weight management on a population level. Combining three U.S. cohorts (together 120 877 humans!) Mozaffarian *et al*. (2012) observed that daily consumption of yogurt was associated with a weight loss of 0.37 kg over a period of 4 years. This weight reducing effect was stronger than for any other food type, including fruits, vegetables, whole grain products and nuts. In this study, different types of yoghurt were not distinguished and the data includes the consumption of plain yoghurt as well as probiotic (including *L. acidophilus*) fortified yoghurt. Intriguingly, other dairy products did not have similar effect as yoghurt, giving a strong hint that the efficacy of the yoghurt in reducing weight loss is not due to the dairy matrix but due to the lactic acid bacteria fermentation.

Conflict of interests

The authors are employees of DuPont. DuPont produces and markets probiotic products.
The Global Alliance of Probiotics consists of Chr. Hansen, Danone, DuPont, Lallemand, Probi, Valio and Yakult.

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