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Short communication on the protective effect of probiotics on type 1 diabetes and obesity diseases

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ABSTRACT
Both diabetes and obesity are life-threatening diseases that put immunity to the test. In this paper, the possibility of using probiotic organisms to control type 1 diabetes (T1D) and obesity is discussed holistically, citing relevant literature that has contributed to this notion. More studies are required using a validation lens to underscore the safety and efficacy of probiotics as agents of change or healing.

KEYWORDS
obesity; type 1 diabetes; probiotics

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INTRODUCTION

Viable and beneficial microorganisms that are responsible for the modulation of bacterial and fungi growth in the intestine are referred to as probiotics [1]. Several of these probiotic organisms and their formulations are commercially available for this purpose, even though in practice, they are widely used despite the lack of a clear indication [2]. Consumption of probiotics is meant to augment the normal intestinal probiotic microbes in a commensal or symbiotic relationship. They contribute to the intestinal microbial balance of the host when they adhere to the gastrointestinal tract surfaces, multiply, colonize and modulate the microbiota [3]. The entire flow ultimately exerts immunomodulatory effects on the gut and the entire body systems due to probiotic competitive suppression of pathogens [4].

In a nutshell, probiotics are potentially therapeutic agents, useful in gut-associated and immune-mediated diseases, thus playing crucial roles that immune-mediated chronic diseases including diabetes and obesity, among others.

EFFECT OF PROBIOTICS ON TYPE 1 DIABETES

Diabetes is a major immune-related disease ever-increasing on a global scale. Type 1 diabetes (T1D) is a disorder that is characterized by insulin-producing pancreatic β-cells destruction, leading to a compromise in the control of blood glucose levels and dependence on exogenous insulin [5].

Other than insulin and proinsulin peptides used as major targets for autoreactive T cells in T1D pathogenesis, human gut microbes have also been investigated where 16S fecal microbiome studies showed a reduced number of Firmicutes but increased number of Bacteroidetes in individuals at the risk of developing T1D [6]. These bacterial deficiencies are associated with the onset and progression of local and systemic inflammatory disorders. Therefore, a cohort study dubbed Environmental Determinants of Diabetes in the Young (TEDDY) involving more than seven thousand genetically-at-risk children of T1D from the United States, Finland, Germany and Sweden, was conducted, and it was found that probiotic supplementation in the infants' feed could potentially reduce the development of islet autoimmunity, as only 8% of the kids developed islet autoantibodies, and particularly those who got the probiotics a year after being born [7].

It was also investigated whether a probiotic combination that had shown immunomodulatory effects on several inflammatory diseases could reduce the incidence of diabetes in non-obese diabetic mice, a classical animal model of human T1D [8]. The probiotics used were *Lactobacillus acidophilus, Lactobacillus casei, Lactobacillus reuteri, Bifidobacterium bifidium*, and *Streptococcus thermophiles*, combined with Immune Regulation and Tolerance 5 (IRT5), and fed to the mice for 8 months.

The investigators found that there was a significant reduction in diabetes incidence and insulitis score, while β-cell mass increased upon IRT5 administration [8]. The study is a preliminary suggestion that probiotics combined with IRT5 might proffer a safe preventive therapy for T1D patients.

It is proposed that in order to progress from animal studies which have already shown consistent results on T2D, multi-center clinical trials under standardized conditions such as the use of certain probiotic strain/combination, determination of its viability, and the optimal dosage, duration, and schedule of therapy need to be conducted [4].

EFFECTS OF PROBIOTICS ON OBESITY

Obesity generally indicates a weight greater than what is considered healthy for a given height and is defined as having a body mass index (BMI) over 30.0 kg/m^2. Obesity is a chronic condition with an excess amount of body fat which notably contributes to the physiopathology of cardiovascular disease and type 2 diabetes (T2D). Hence, this condition promotes chronic inflammation that is mediated by M1-type adipose tissue macrophages, Th1 cells, and CD8 T cells, ultimately leading to reduction of insulin sensitivity and development of T2D [9].

Repeated studies have proven that a major predisposing factor to this disease underlay gut microbiota dysbiosis that creates a major shift in obese people's immune response [10]. After several failed attempts to study the relationship of obesity with the upper gut microbiota, it was later observed that the microbial composition of the lower gut of non-obese individuals had lower Firmicutes/Bacteroidetes ratio and lower *Methanobrevibacter smithii* when compared with those of obese individuals [11]. Hence, this suggests that the lower gut microbial populations could play a role in obesity-related conditions [12]. Thus, several intestinal microbial metabolites such as 10-hydroxy-cis-12-octadecenoic acid, indole, and butyrate were suggested to reverse thermogenesis, a phenomenon associated with adipose tissue regulation, but limited in obese individuals [13,14]. However, Fitzgibbon and Mills [15] recently suggested that FMT could have a therapeutic effect on individuals suffering from insulin resistance-related metabolic disorders, as obesity is a reflection of altered gut microbiota.

Moreover, a study with diet-induced obesity (DIO) in mice showed that supplementation with the anti-inflammatory extracellular polymeric substances-producing probiotic strain L*. casei* LC-XCAL™ significantly reduced hepatic triglycerides, hepatic total cholesterol, and fat pad weight compared to control mice, likely as a result of reduced energy absorption from food [16]. However, 16-S rRNA amplicon analysis of the fecal microbiota of these mice indicated that the altered metabolic phenotype as a result of the probiotic supplementation was not associated with an overall change in the composition or inferred functional capacity of the fecal microbiota despite some abundance changes in individual taxa and functions [16].

Obesity also has ties with circulating molecules such as leptin. This condition may be ameliorated using probiotics, whose purpose is to suppress the leptin levels via gut microbiota alteration. For example, *Lactobacillus rhamnosus* GG (LGG) was tested for its effects on gut microbiota and modulation of leptin resistance in male BALB/c mice aged 7 weeks fed either a normal diet, high-fat diet (HFD), HFD supplemented with low-dose LGG (108 CFU/mouse/day), or HFD supplemented with high-dose LGG (1010 CFU/mouse/day) for 10 weeks [17]. The investigators found that the body weight, epididymal fat weight, and decreased leptin responsiveness to exogenous leptin treatment and the ratio of villus height to crypt depth, significantly increased in HFD-fed mice as compared to the control mice, as well as a remarkable increase in the proportion of Proteobacteria and ratio of Firmicutes/Bacteroidetes in the fecal microbiota [17]. In addition, HFD supplemented with high-dose LGG restored exogenous leptin responsiveness, increased the ratio of villus height to crypt depth, and decreased the proportion of Proteobacteria in fecal microbiota [17]. Therefore, the findings showed that high-dose of probiotic LGG might restore the responses of exogenous leptin by alleviating the resistance created by HFD *via* host gut health enhancement.

Many other very recent studies indeed showed interesting mechanistic immunomodulatory effects of probiotics either used alone or in combination with other parameters on obesity. They include the use of *L. plantarum* CQPC03 to regulate lipid metabolism in the liver and serum of HFD-induced obesity in mice [18], the anti-obesogenic activities of *Akkermansia*

muciniphila strains isolated from human stool samples, and their relationship with the gut microbiota in HFD-fed mice [19], the probiotic supplementation to bariatric surgery patients to lose weight and alleviate some gastrointestinal symptoms, with minor or no adverse events [20], and the effects of selenium-enriched Bifidobacterium longum DD98 (Se–*B. longum* DD98) on metabolic alterations and liver injuries associated with obesity in HFD-fed mice, by balancing hepatic lipid disorder and suppression of liver steatosis [21]. Other investigations include evaluation of *Enterococcus faecalis* AG5 and its metabolites to regulate energy homeostasis, as the probiotic AG5 remarkably reduced body weight, BMI, serum cholesterol, triglycerides, LDL, and VLDL alongside adipocyte hypertrophy and fatty acid accumulation while improving HDL, insulin, and leptin [22]. The cell-free metabolites of *L. plantarum* inhibited the differentiation of 3T3-L1 adipocytes and fat depositions via down-regulation of the key adipogenic transcriptional factors (PPAR-gamma, C/EBP-alpha, and C/EBP-beta) and their downstream targets (FAS, aP2, ACC, and SREBP-1) while reducing the fat mass and serum lipid profile concurrently with down-regulation of lipogenic gene expression in the adipocytes, resulting in reductions in the bodyweight of HFD-fed obese mice [23]. In this study, the probiotic mechanisms clearly indicated alleviation of obesity *via* the inhibition of PPAR gamma through activation of the p38MAPK and p44/42 signaling pathways [23]. Lastly, a similar study on probiotic metabolites connoted that bacteriocin PJ4 from *Lactobacillus* spp. could reduce adipokine and inflammasome in HFD-induced obesity [24].

It is therefore deduced from the results that specific microbes and careful selection of appropriate probiotic strains may path the way to effectively modulate metabolic issues. The point is that lower gut microbes such as Firmicutes/Bacteroidetes and *Methanobrevibacter smithii*; several intestinal microbial metabolites such as 10-hydroxy-cis-12-octadecenoic acid, indole, and butyrate; circulating molecules like leptin; and FMT strategies could play a role in obese subjects. Therefore, the administration of probiotic strains might also aid to counteract obesity alterations and are thus emerging as modulatory and therapeutic agents against this global disease.

CONCLUSIONS

It is indeed a possible, attainable, and obviously proven notion that probiotic organisms have protective effects on type 1 diabetes and obesity diseases, which are not only chronic but global health challenges. More studies are required using a validation lens to underscore the safety and efficacy of probiotics as agents of change or healing

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