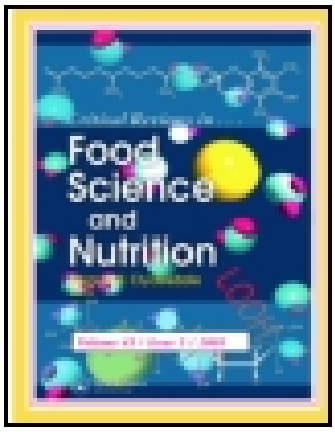

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Evidence for the Effects of Yogurt on Gut Health and Obesity

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Title: Evidence for the effects of yogurt on gut health and obesity.

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Abstract:

Obesity is associated with increased risk for chronic diseases, and affects both developed and developing nations. Yogurt is a nutrient-dense food that may benefit individuals with lactose intolerance, constipation and diarrheal diseases, hypertension, cardiovascular diseases, diabetes and certain types of cancer. Emerging evidence suggests that yogurt consumption might also improve the health of obese individuals. Obesity is often accompanied by chronic, low-grade inflammation perpetuated by adipose tissue and the gut. In the gut, obesity-associated dysregulation of microbiota and impaired gut barrier function may increase endotoxin exposure. Intestinal barrier function can be compromised by pathogens, inflammatory cytokines, endocannabinoids, diet, exercise, and gastrointestinal peptides. Yogurt consumption may improve gut health and reduce chronic inflammation by enhancing innate and adaptive immune responses, intestinal barrier function, lipid profiles, and by regulating appetite. While this evidence suggests that yogurt consumption is beneficial for obese individuals, randomized-controlled trials are needed to further support this hypothesis.

Keywords: yogurt; obesity; inflammation; intestine; chronic disease; bioactives

INTRODUCTION

Yogurt has been consumed for centuries. As early as 1908, Metchnikoff ascribed the prolonged life of the Bulgarians to consumption of sour milk fermented by lactic acid bacteria (O'Sullivan et al., 1992). Yogurt is a milk product fermented by *L. bulgaricus*, *S. thermophilus* and *L. acidophilus* (CODEX STAN 243-2003). In addition to these Lactic acid bacteria (LAB), other strains of *Lactobacillus* and *Bifidobacterium* are commonly used as yogurt starter cultures (Desobry-Banon et al., 1999). Yogurts may also be enriched in other probiotic strains that convey additional health benefits beyond those of traditional yogurt cultures (Shah, 2007).

The global rise in obesity is an increasing health concern. The causes of obesity and approaches needed to reduce obesity are multifactorial in nature (Holes-Lewis et al., 2013). Effective social, behavioral, and dietary interventions are needed to mitigate the adverse effects of obesity on personal health outcomes (Wadden et al., 2012). Obesity impairs gut health, which may be a potential target for therapeutic dietary interventions (Tilg and Kaser, 2011). Yogurt is rich with potential bioactive components and emerging evidence points toward the efficacy of yogurt and its components to improve gut health in obesity.

YOGURT BIOACTIVES

Nutrients

Dairy products are rich in high-quality proteins, calcium, potassium, phosphorus, magnesium, zinc and B vitamins (**Table 1**) (Buttriss, 1997). Fermentation can improve the nutrient content of dairy products. For example, some bacteria synthesize B vitamins. *S. thermophilus* can produce folate during yogurt fermentation, and certain inoculations can increase folate levels 6-fold (Crittenden et al., 2003). Yogurt also contains conjugated linoleic

acid (CLA), a derivative of linoleic acid (Aneja and Murthi, 1990; Shahani and Chandan, 1979). CLA may improve body composition by increasing lean body mass while decreasing fat mass, and has immunostimulatory and anticarcinogenic effects (Park et al., 1997; Whigham et al., 2000).

Fermentation also improves the digestibility of milk proteins. LAB proteolytic enzymes and peptidases increase free amino acids in yogurt (Gorbach, 1990). Upon digestion, yogurt had smaller clots of curd than milk, which facilitated digestive enzyme activity (Breslaw and Kleyn, 1973). In addition, the viscous texture of yogurt might decrease the gastric emptying rate, which increases duration of the enzymatic hydrolysis (Gaudichon et al., 1994; Shahani and Chandan, 1979).

Yogurt is also considered to be a good source of minerals. Dairy products are a good source of calcium, not just because of the abundance of calcium but also because of the high absorbability of calcium from yogurt. The presence of lactose, phosphopeptides, and amino acids derived from casein in dairy products facilitates the absorption of calcium by promoting its active transport or passive diffusion (Gueguen and Pointillart, 2000). However, intervention studies have not demonstrated greater bioavailability of dairy calcium than supplemental calcium (Recker et al., 1988; Sheikh et al., 1987; Zhao et al., 2005). In contrast, dairy calcium was more effective than supplementary calcium in reducing weight and fat in energy-restricted adults (Zemel et al., 2000; Zemel et al., 2004). Although there is no evidence showing that yogurt serves as a better source of calcium than milk or other dairy products, yogurt has the advantage of being well tolerated by lactase-deficient individuals (Smith et al., 1985).

Other bioactives

Dairy products contain bioactive proteins, such as immunoglobulins, Ŭ-lactoglobulin, ɓ-lactoglobulin, lactoferrin, and phosphopeptides, which may regulate immune response, modulate blood pressure, and facilitate mineral absorption (Ebringer et al., 2008). Bacterial hydrolysis of milk protein can yield oligopeptides with additional biological activities. For instance, some peptides (e.g. Val-Pro-Pro and Ile-Pro-Pro) have hypotensive effects via inhibiting angiotensin-converting-enzyme (Nakamura et al., 2009). A pentapeptide hydrolyzed from casein, Ile-Ile-Ala-Glu-Lys, has hypocholesterolemic effects *in vitro* (Morikawa et al., 2007). Other effects of bioactive peptides such as antithrombotic, antioxidant, antimicrobial and antifungal activities have also been reported (Ebringer et al., 2008).

Dairy products also contain various bioactive lipids and oligosaccharides. Phospho- and sphingolipids may reduce blood cholesterol, enhance brain function, and inhibit colon cancer (Ebringer et al., 2008; Rombaut et al., 2005). Some short chain fatty acids in dairy products such as butyric acid (C4:0), caprylic acid (C8:0), capric acid (C10:0), lauric acid (C12:0) have anticarcinogenic, antiviral and antibacterial activities (Ebringer et al., 2008). In addition, dairy products contain some oligosaccharides such as lactulose, which could serve as prebiotics to support the growth of commensal bacteria (Marconi et al., 2004).

Microorganisms

S. thermophilus and *L. bulgaricus* are the most frequent microorganisms used to produce yogurt. In the United States, some yogurts have additional *L. acidophilus*, *B. bifidum, B. lactis, L. casei,* and/or *L. rhamnosus* content, among others, and are branded as ǵprobiotic yogurts.ô The most basic definition of probiotics is, ñlive microorganisms which when administered in adequate amounts confer a health benefit on the hostò (Pineiro and Embarek, 2002). However,

others have proposed that probiotics must originate from humans, be viable through the gastrointestinal tract, adhere to the intestinal wall to facilitate colonization, produce antimicrobials, and provide a demonstrable health effect (Guarner et al., 2005).

It is commonly thought that 10^5 - 10^7 CFU/mL living probiotic bacteria are needed to confer a health benefit to the host (Schillinger, 1999; Vélez et al., 2007). Yogurt culture content ranges from 10^4 to 10^8 CFU/g/strain (Dunlap et al., 2009). In the US, yogurt can be certified with a ñlive and active cultureò seal from the National Yogurt Association if it contains 10^8 CFU/g at the time of manufacture (National-Yogurt-Association, 2008). While the viability of yogurt microorganisms may be enumerated at manufacture, viability declines throughout the shelf-life of products. For example, *L. acidophilus,* a culture commonly added to yogurt post-fermentation, is relatively unstable in yogurt. This is likely due to hydrogen peroxide produced by *L. bulgaricus* during yogurt production (Gilliland and Speck, 1977). A survey of yogurts in Columbia found poor survival and inconsistent labeling of strains (Vélez et al., 2007). In a study of yogurts of European origin, bacterial counts in some products were as low as 10^4 CFU per gram per strain by the sell-by date (Schillinger, 1999). Temperature fluctuations may also reduce viability of yogurt probiotics. After 6 h at room temperature, reductions of 9-46.2% were seen in the CFU count for *L. GG, L. johnsonii,* and *L. acidophilus* (Scharl et al., 2010). Thus, it is expected that the amount of traditional and probiotic strains present in yogurt varies considerably by manufacturer, storage conditions, and time of consumption. Despite this, yogurt cultures may not need to be viable to confer a health benefit. For example, a preparation of mixed DNA from various probiotic strains inhibited colitis in IL-$10^{-/-}$ mice (Jijon et al., 2004). Conventional yogurt

LAB improve lactose digestion, despite poor viability and the inability to survive the digestive process (Martini et al., 1991).

OBESITY, YOGURT AND CHRONIC DISEASE RISK

Obesity is an abnormal or excessive accumulation of fat that poses a risk to health. A person with a body mass index (BMI) between 25 and 30 is classified as overweight and a BMI greater than 30 is obese. The International Obesity Task Force estimates that at least 1.1 billion adults are overweight, with 312 million of those obese (Haslam and James, 2005). In the US, nearly 70% of adults are classified as overweight or obese (Flegal et al., 2010). Obesity is a major risk factor for a number of chronic diseases such as diabetes, cardiovascular disease (CVD) and certain cancers. Furthermore, obese adults are projected to lose 7 years of life expectancy (Peeters et al., 2003). The morbidity associated with obesity accounts for 2-7% of health care costs in the developed world (Hossain et al., 2007). Morbidities attributed to obesity include CVD, type 2 diabetes, hypertension, cancer, chronic inflammation, and compromised gut health. A limited number of yogurt intervention studies relevant to obesity and chronic disease risk have demonstrated positive outcomes on lipid profiles and chronic inflammation (**Table 2**).

Cardiovascular disease

CVD is one of the leading causes of death and premature mortality. Ischaemic heart diseases and stroke account for nearly one in four deaths worldwide (Lozano et al., 2012). Visceral obesity has a critical role in the development of CVD (Grundy, 2007). Mathieu et al. reviewed how inflammation linked obesity and CVD (Mathieu et al., 2010). Briefly, excessive accumulation of fat in the adipose tissue leads to macrophage infiltration and elevated production of proinflammatory cytokines, which contribute to the development of atherosclerosis. In

addition, obesity is related to atherogenic dyslipidemia characterized by increased levels of triglyceride (TG), small dense low-density lipoprotein (sdLDL) particles, as well as decreased level of high-density lipoprotein cholesterol (HDL-C) (Tenenbaum and Fisman, 2012). Obesity can also directly affect the structure and functions of the cardiovascular system. Obese individuals have increased cardiac output which can lead to left ventricular hypertrophy and other structural abnormalities (Lavie et al., 2009). Obesity also causes left atrial enlargement due to increased circulating blood volume and abnormal left ventricular diastolic filling (Lavie et al., 2009). These abnormalities compromise cardiovascular function and increase CVD risk for obese individuals (Lavie et al., 2009).

Several recent expert reviews have summarized the potential benefits of dairy consumption on CVD risk. Van Meijl et al. reviewed the physiological effects of dairy consumption on metabolic syndrome and concluded that dairy calcium and protein had important roles in reducing metabolic syndrome risk (Van Meijl et al., 2008). In a prospective, matched case-control study using serum milk fat biomarkers, it was found that biomarkers of milk fat were inversely associated with the first myocardial infarction in Swedish women after multivariable adjustment for confounders (OR 0.74, 95% CI: 0.58, 0.94); moreover, reported intake of fermented milk products were inversely related to the first myocardial infarction ($P <$ 0.05 for trend) (Warensjö et al., 2010). German et al. reviewed the effects of dairy foods and dairy fats on CVD risk (German et al., 2009). They suggested that although dairy products contributed to saturated fat intake, there was no consistent association between dairy consumption and risk of CVD (German et al., 2009). Similarly, another group examined the influence of milk fat containing dairy foods and CVD health and concluded that dairy

consumption did not increase the risk of CVD, coronary heart disease or stroke, regardless of milk fat levels (Huth and Park, 2012). Most research on dairy and CVD risk have not evaluated yogurt specifically. Given the differences in nutrient and bioactive content between yogurt and other dairy products, more attention is needed on this specific product category.

Conventional yogurt consumption may improve lipid profiles in healthy and hypercholesterolemic adults. The effects of conventional yogurt, yogurt with *L. acidophilus* and *B. lactis,* or no yogurt on blood lipids were evaluated in healthy Iranian women (n = 90) (Sadrzadeh-Yeganeh et al., 2010). Consumption of 300 g/d of conventional and probiotic yogurt for 6 wk reduced the total cholesterol and total:HDL cholesterol ratio relative to the control group (Sadrzadeh-Yeganeh et al., 2010). The probiotic yogurt-consuming group also experienced an 8.8% increase in HDL cholesterol (Sadrzadeh-Yeganeh et al., 2010). Probiotic or prebiotic containing yogurt may also further improve lipid profiles in adults. A randomized cross-over study of 40 hypercholesterolemic US adults consuming 200 g yogurt with *L. acidophilus* L1 for 4 wk reduced serum cholesterol by 3.2% relative to a yogurt prepared with an *L. acidophilus* strain with poor viability and low *in vitro* cholesterol-lowering activity (Anderson and Gilliland, 1999). In a cross-over study of 29 healthy women, which included hypercholesterolemic individuals, 300 g of yogurt with *L. acidophilus* and *B. longum* for 7 weeks increased serum HDL cholesterol by 0.3 mmol/L relative to a control yogurt without these strains (Kießling et al., 2002). In a parallel study of 33 normocholesterolemic women, consumption of 100 g/d yogurt for 2 wk and 200 g/d for another 2 wk reduced the LDL/HDL cholesterol ratio in healthy women, with no differences from the probiotic culture *L. casei* containing yogurt (Fabian and Elmadfa, 2006). Consumption of 375 mL of yogurt containing *L.*

acidophilus and fructo-oligosaccharides for 3 wk lowered serum total cholesterol, LDL-cholesterol, and the LDL/HDL-ratio in 30 healthy men relative to conventional yogurt (Schaafsma et al., 1998).

Hypertension

Hypertension is associated with vascular disease mortality, CVD, and renal diseases (Chobanian et al., 2003; Lewington et al., 2002). Hypertension in US adults increased from 23.9% in 1988-1994 to 29% in 2007-2008 based on data from the National Health and Nutrition Examination Survey (NHANES) (Egan et al., 2010). Previous studies have indicated a strong relationship between obesity and hypertension. Cross-sectional studies indicate that more than 85% of hypertensive individuals have a BMI of over 25 kg/m^2 (Kastarinen et al., 2000). Several mechanisms are involved in the pathogenesis of obesity-related hypertension. The sympathetic nervous system, the renin-angiotensin system (RAS), and aldosterone contribute to the development of hypertension in obesity (Rahmouni et al., 2005). Long-term over-activation of sympathetic nervous system which is found in obesity could raise arterial pressure by inducing peripheral vasoconstriction and increasing sodium reabsorption in the renal tubules (Rahmouni et al., 2005). Adipose RAS is activated in obesity; animal models of visceral obesity suggest that adipose RAS contributes to obesity-associated hypertension (Massiéra et al., 2001). Plasma aldosterone levels were elevated in obese hypertensive patients (Goodfriend and Calhoun, 2004); on the other hand, an aldosterone antagonist was found to inhibit the development of high blood pressure in dietary-induced obese dog models (De Paula et al., 2004).

Therefore, given the need for dietary strategies to mitigate hypertension, the antihypertensive effects of dairy consumption have been investigated. The Dietary Approaches

to Stop Hypertension (DASH) trial showed that a diet rich in fruits and vegetables lowered blood pressure and that additional inclusion of low-fat dairy products with reduced saturated and total fat further augmented these blood pressure-lowering effects (Appel et al., 1997). A recent review and meta-analysis of five cohort studies involving nearly 45,000 subjects revealed an inverse association between dairy consumption and development of elevated blood pressure, defined as Ó130 mm Hg systolic and/or Ó84 mm Hg diastolic blood pressure (RR 0.87, 0.81-0.94 95% CI) (Ralston et al., 2012). Another meta-analysis of prospective cohort studies similarly reported that increased consumption of 200 g/d of low-fat dairy products reduced the risk of hypertension (RR 0.96, 95% CI, 0.93-0.99) (Soedamah-Muthu et al., 2012). Based on these data, low-fat dairy consumption appears protective against hypertension in adults, but well-designed randomized, controlled trials (RCTs) are needed to confirm if yogurt is also antihypertensive.

Cancer

In 2010, 8 million people died from cancer globally, accounting for 15.1% of all deaths worldwide (Lozano et al., 2012). Overweight and obesity are estimated to contribute to 14% of all cancer deaths in men and 20% of deaths in women (Calle et al., 2003). Meta-analyses indicate that higher BMI is associated with an increased incidence of endometrial, colorectal, and postmenopausal breast cancer (Larsson and Wolk, 2007; Moghaddam et al., 2007; Reeves et al., 2007). It is hypothesized that obesity disturbs the physiological function of adipose tissue, which leads to insulin resistance, chronic inflammation, and dysregulation of adipokine secretion, factors contributing to the promotion and progression of cancer (Van Kruijsdijk et al., 2009). Accumulating evidence indicates potential beneficial effects of yogurt consumption on cancers. A prospective study involving 82,220 Swedish individuals found that the risk for bladder cancer

was lowest in individuals consuming the highest levels of sour milk and yogurt (RR 0.62, 95% CI, 0.46-0.85; Ó2 servings/d vs. 0 serving/d) (Larsson et al., 2008). In another prospective study in an Italian cohort involving 45,241 volunteers, after adjusting for energy, simple sugar, calcium, fiber, animal fat, alcohol and red meat intake, body mass index, smoking, education, and physical activity, the hazard ratio for colorectal cancer in the highest versus lowest tertile of yogurt intake was 0.65 (95% CI, 0.48-0.89) (Pala et al., 2011). Animal studies support the beneficial effects of yogurt. For example, LABs from yogurt were shown to effectively inhibit the genotoxic effects of heterocyclic aromatic amines on rats (Zsivkovits et al., 2003). *L. acidophilus* isolated from yogurt reduced tumor growth rate and increased lymphocyte proliferation in a mouse model of breast cancer (Maroof et al., 2012). A potential mechanism for reduced cancer risk is lower fecal mutagenicity, as demonstrated by consumption of yogurt with *B. lactis* by elderly individuals (Matsumoto et al., 2001). Given these promising results for yogurt intake and reduced risk for bladder and colon cancers, further work is warranted to evaluate if yogurt is similarly protective against other cancers.

Diabetes

The worldwide prevalence of diabetes in adults was estimated at 6.4% in 2010, and is projected to increase to 7.7% by 2030 (Shaw et al., 2010). Excess weight may contribute to 90% of type 2 diabetes cases (Hossain et al., 2007). More than 197 million people worldwide have impaired glucose tolerance attributed to obesity or metabolic syndrome (Hossain et al., 2007). Many studies have illustrated the mechanisms linking obesity and type 2 diabetes. Adipose tissue has a pivotal role in type 2 diabetes by releasing non-esterified fatty acids (NEFAs), hormones, and various proinflammatory cytokines (Shoelson et al., 2006). Overabundant intracellular

NEFAs inhibit key enzymes involved in glucose metabolism (Kahn et al., 2006). Furthermore, the corresponding intracellular fatty acid metabolites activate the serine/threonine kinase cascade which disturbs the insulin signaling pathway (Shulman, 2000). To compensate for insulin resistance, the pancreatic ϐ-cells secrete more insulin, eventually causing endoplasmic reticulum stress and protein misfolding which lead to ϐ-cell apoptosis (Muoio and Newgard, 2008).

Dairy consumption may reduce risk of type 2 diabetes. For example, an 8 yr prospective cohort study of 82,076 postmenopausal women demonstrated that low-fat dairy products were inversely associated with the risk of type 2 diabetes (RR 0.65; 95% CI: 0.44-0.96 for the highest quintile of intake) (Margolis et al., 2011). A recent meta-analysis of cohort studies showed that the adjusted relative risk of type 2 diabetes for highest versus lowest quartiles of dairy intake was 0.86 (95% CI, 0.79-0.92) (Tong et al., 2011). A subgroup analysis revealed a relative risk of 0.83 (95% CI, 0.74-0.93) for the intake of yogurt (Tong et al., 2011). A newer prospective study including 340,234 subjects did not find an association between total dairy products and diabetes. However, in the dairy subtype analysis, a higher combined intake of fermented dairy products (cheese, yogurt and thick fermented milk) was inversely associated with diabetes (HR, 0.88; 95% CI, 0.79-0.99) (Sluijs et al., 2012). In another smaller-sized prospective study, fermented dairy intake was inversely associated with fasting plasma glucose and HbA_{1c}, although no significant association between intake and incidence of diabetes was found (Sluijs et al., 2012). Although epidemiological studies support the beneficial effects of yogurt consumption on reduced type 2 diabetes risk, RCTs are needed to confirm the causal effects of dairy consumption on improved diabetes outcomes.

OBESITY, YOGURT AND CHRONIC INFLAMMATION

The anti-inflammatory effects of low-fat dairy products have been well documented (Sakamoto et al., 2001; Schiffrin et al., 2009; Yang and Sheu, 2012). Inflammation is characterized by redness, swelling, heat, and pain and is typically resolved shortly after the insult or stimuli are removed (Hotamisligil, 2006). In contrast, obesity-associated chronic inflammation is unresolved, low-grade inflammation that originates from metabolic cells (e.g. adipocytes) in response to excessive nutrient intake (Gregor and Hotamisligil, 2011). Overactive metabolic signals induce the activation of proinflammatory pathways, which cause low-level induction of cytokines in metabolic tissues; these inflammatory signals recruit immune cells into metabolic tissues and disrupt the normal metabolic cell functions (Gregor and Hotamisligil, 2011).

Obesity leads to increased levels of inflammatory biomarkers in a variety of tissues (**Table 3**). For example, protein kinases such as JNK and inhibitor of ə kinase (IKK) induce the expression of proinflammatory cytokines (Solinas and Karin, 2010). Obese women had a significantly higher amount of phosphorylated (active form) JNK in omental fat compared with lean women (Bashan et al., 2007). In rodents, Hirosumi et al. observed significant increases in total JNK activity in liver, muscle and adipose tissues of both dietary and genetic (ob/ob) obesity models (Hirosumi et al., 2002). Increased activation of JNK and NF-əB pathways were also detected in the hypothalamus of high-fat-fed mice, accompanied by increased secretion of proinflammatory cytokines (De Souza et al., 2005). Elevated NF-əB and IKK activities were found in the livers of both genetic and diet-induced obese mice (Cai et al., 2005). In high-fat-fed mice, increased IKK activity and downstream products of NF-əB pathway were observed in lysates of the thoracic aorta (Kim et al., 2007). Therefore, the metabolic and inflammatory consequences of obesity affect a wide variety of tissues. Animal and a limited number of human

studies indicate a potential role for dairy or yogurt consumption to mitigate chronic inflammation associated with obesity, as detailed below.

Increased infiltration of immune cells into metabolic tissues

Obesity increases the infiltration of immune cells into various metabolic tissues. Macrophages infiltrate adipose tissue in obese individuals and are responsible for nearly all adipose-derived TNF-Ŭexpression (Weisberg et al., 2003). Similarly, obesity leads to increased inflammatory macrophages in visceral adipose tissue (Curat et al., 2006). Macrophage-derived proinflammatory cytokines can subsequently initiate insulin resistance and compromise ɓ-cells (Solinas and Karin, 2010).

Animal models of obesity corroborate the infiltration of macrophages and other immunocytes. Macrophages and microphages were increased in white adipose tissue in both genetic and high-fat diet-induced models of obese mice (Xu et al., 2003). Ehses et al. observed increased islet-associated macrophages in high-fat-fed mice and *db/db* obese mice (Ehses et al., 2007). Diet-induced obese mice had increased accumulation of T cells in adipose tissue relative to lean mice (Wu et al., 2007). Likewise, natural killer T (NKT) cells infiltrated visceral adipose tissue in high-fat-fed mice (Ohmura et al., 2010). In the same model, depletion of NKT cells ameliorated visceral adipose tissue inflammation (Ohmura et al., 2010).

Yogurt and LAB can modulate the immune response through cytokine production. However, studies have not focused on the role of yogurt or dairy on obesity-associated immunocyte dysregulation. In diet-induced obese mice, compared to the high calcium diet, a nonfat dry milk-supplemented diet reduced weight gain and associated adipose tissue inflammation as shown by decreased mRNA abundance of (monocyte chemoattractant protein)

MCP-1, TNF-Ŭ, and IL-6; this suggested that some active components in dairy other than calcium could modulate the immune response (Thomas et al., 2012).

Yogurt and its associated cultures also have immunostimulatory effects in healthy individuals. Consumption of yogurt containing *L. bulgaricus* and *S. thermophilus* increased production of IFN-ɔ by T cells in young adults (Halpern et al., 1991). IFN-ɔ regulates the induction of pro-inflammatory cytokines and the activation of macrophages and natural killer cells. LAB directly stimulates human lymphocyte IFN-ɔ *in vitro* (De Simone et al., 1986). An observational retrospective study showed that supplementation with yogurt containing *L. rhamnosus* increased the CD4 count in a group of people living with HIV (Irvine et al., 2010). Consumption of fermented milk containing *L. acidophilus* significantly increased the phagocytosis of *E. coli* in adults (Schiffrin et al., 1997). Likewise, fermented milk with *L. casei*, *L. acidophilus,* or a mixture of both increased phagocytic lymphocytic activities in Swiss mice (Perdigon et al., 1995). Oral administration of *L. acidophilus* alone improved immunoreactivity of peripheral blood leukocytes and peritoneal phagocytes and enhanced serum antibody response to orally and systemically administrated antigens in mice (Gill et al., 2000). Since yogurt consumption in obese individuals does not produce pro-inflammatory effects (Labonté et al., 2013), further work is needed to identify how yogurt modulates immune cells in obesity, and whether these effects are localized to the gut or have broader activities at metabolic tissues.

OBESITY, YOGURT, AND INTESTINAL BARRIER FUNCTION

The chronic inflammation associated with obesity may be exacerbated by impaired intestinal barrier function. Leptin-deficient and hyperleptinemic obese mice have increased intestinal permeability, modified distribution of junction proteins in the intestinal mucosa, as

well as increased circulating levels of inflammatory cytokines compared with lean control mice (Brun et al., 2007). Diet-induced obese mice fed high-fat diets had increased intestinal permeability assessed by gavage of fluorescent-dextran, increased plasma LPS levels, and reduced expression of genes for tight junction proteins (Cani et al., 2008). Obese women had increased paracellular permeability measured by lactulose excretion relative to lean women (Teixeira et al., 2012). Intestinal paracellular permeability was correlated with waist circumference and HOMA values (Teixeira et al., 2012). Likewise, intestinal barrier function was more strongly correlated with central adiposity than BMI in overweight adults (Gummesson et al., 2011). Dysregulation of intestinal barrier function may be attributed to dysregulation of gut microbiota, endotoxin exposure, the mucus bilayer, secretory immunoglobulin A (sIgA), antimicrobial peptides, and tight junction proteins. Emerging evidence supports the ability of yogurt consumption to modulate these functions, as discussed below.

Dysregulation of gut microbiota

The intestine is essential for nutrient absorption and host defense. Gut microbiota facilitate these functions by fermenting non-digestible nutrients, vitamin synthesis, and participating in host defense (Salzman et al., 2007). Favorable gut microbiota may compete with pathogens for space and nutrients and produce anti-microbial compounds such as bacteriocins and lactic acids (O'Hara and Shanahan, 2006). Gut microbiota also contribute to energy homeostasis and fat storage. Interestingly, germ-free mice were protected against diet induced obesity (Bäckhed et al., 2007). On the other hand, conventionalization of germ-free mice with a normal microbiota harvested from the cecum of conventionally raised mice caused a 60% increase in body fat within 14 d despite reduced food consumption (Bäckhed et al., 2004). The

authors proposed that the gut microbiota helped to absorb monosaccharides from the lumen which further induced de novo hepatic lipogenesis (Bäckhed et al., 2004). Colonization of germ-free mice with microbiota from obese mice induced a more significant increase in total body fat than colonization with microbiota from lean mice (Turnbaugh et al., 2006). This suggested that the composition of gut microbiota affects the development of obesity. In both mice and humans, *Bacteroidetes* and *Firmicutes* are the major species comprising the microbiota (Bäckhed, 2009). Obese adults have a lower proportion of *Bacteroidetes* to *Firmicutes* than lean, although this ratio can be improved with weight loss from energy restriction (Ley et al., 2006).

Conventional yogurt cultures have limited viability in the gut and a limited ability to influence the composition of the gut microbiota. Adults consuming yogurt with *S. thermophilus* and *L. bulgaricus* had less than 10^3 CFU/g of these cultures in feces (Del Campo et al., 2005). In another study, participants consumed 125 g of a commercial yogurt twice per day for one week, providing 10^8 CFU of *S. thermophilus* and *L. bulgaricus* (Elli et al., 2006). *S. thermophilus* was not present in feces, although *L. bulgaricus* was present in about 70% of the fecal samples provided on days 2 and 7 of the yogurt-consumption period. However, the levels of *L. bulgaricus* detected on average did not exceed the 10^5 CFU/g minimum deemed necessary to exert beneficial effects (Elli et al., 2006). Another study providing a higher dose of yogurt cultures (375 g yogurt, 10^8 CFU/g) for two weeks, reported a median value of approximately 10^4 CFU each of *S. thermophilus* and *L. bulgaricus* per gram of feces (Mater et al., 2005). Although yogurt cultures have apparently low viability through the entire gastrointestinal tract, more information is needed about their small intestine viability.

Certain probiotic strains may have improved viability in the gut relative to *S. thermophilus* and *L. bulgaricus*. Healthy adults that consumed 230 mL yogurt with additional *L. acidophilus* and *B. bifidum* at 10^7 CFU/g daily for 10 days had decreased aerobic bacteria and increased anaerobic bacteria in fecal samples (Chen et al., 1999). Additionally, the bifidus to coliform ratio favorably increased and *B. bifidum* was measurable for up to 8 days after consumption (Chen et al., 1999). In contrast, *L. acidophilus*, *S. thermophilus,* and *L. bulgaricus*, were not detectable in feces (Chen et al., 1999).

McNulty et al (2011) investigated the effect of *B. animalis* subsp. *lactis* on the gut microbiota of mice and humans. Healthy pairs of monozygotic twins consumed a fermented milk product (FMP) with *L. bulgaricus* and *B. animalis* subsp. *lactis* or no product daily for seven weeks. Fecal samples analyzed before, during, and after the intervention did not show a statistically significant change in the microbiota composition (McNulty et al., 2011). Additionally, the FMP cultures did not persist in the microbiota longer than two weeks after ceasing its consumption. In the same study, human-gut-derived bacterial strains and FMP strains were transplanted into germ-free mice. Similar to humans, the humanized intestinal microbiota was not drastically altered by FMP, but genes related to carbohydrate metabolism were up-regulated by FMP consumption (McNulty et al., 2011).

Animal models suggest that yogurt-induced improvements in intestinal permeability are associated with changes to gut microbiota. In Wistar rat pups, consumption of yogurt with *L. casei* counteracted acute gastroenteritis-induced barrier dysfunction (Isolauri et al., 1993). In atopic dermatitis (AD) patients with increased intestinal permeability, 4 wk consumption of yogurt with *B. lactis*, *L. bulgaricus,* and *S. thermophilus* increased polyamine-producing

bacterial species which was associated with improved intestinal barrier function (Matsumoto et al., 2007).

Cultures used in yogurt may also be modified to improve their viability in the gut by protecting cultures from stomach acid. For example, yogurt with encapsulated or free *L. acidophilus* ATCC 4356 was subjected to a simulated human digestive system (Ortakci and Sert, 2012). Encapsulated *L. acidophilus* had improved viability up to 2 h of incubation in artificial human gastric juice.

Thus, conventional yogurt cultures have low to no viability in the gut. Probiotic or encapsulated strains may have greater viability, and their metabolic effects or competition with coliforms in the intestine are apparent. These studies suggest that strains may not need to adhere to the intestinal epithelium and proliferate in order to exert the desired health effects. If this is the case, it suggests that consistent and prolonged probiotic consumption may be needed to achieve measurable health benefits from these strains.

Contribution of bacterial endotoxin to chronic inflammation

Gut microbiota contribute to systemic low-grade inflammation by increasing the exposure to proinflammatory bacterial products, especially the Gram-negative-derived LPS among others (Okamura et al., 2001; Rallabhandi et al., 2006). LPS typically consists of a hydrophobic domain known as lipid A, a non-repeating core oligosaccharide, and a distal polysaccharide (Raetz and Whitfield, 2002). LPS initiates inflammatory signaling through LPS binding protein (LBP), CD14, Toll-like receptor-4 (TLR-4) and MD-2. LBP is thought to extract LPS and subsequently deliver it to CD14 or lipoprotein; the former may lead to the activation of target cells while the latter may result in the clearance by liver (Van Bossuyt et al., 1988). CD14

serves as a pattern-recognition receptor in proinflammatory signaling which can be stimulated by various ligands (Park et al., 2009; Pugin et al., 1994). MD-2 physically associates with TLR-4 on the cell surface and acts as co-receptor with TLR-4 for the detection of LPS (Manco et al., 2010). Once activated by LPS, TLR-4 undergoes oligomerization and recruits its two adaptor protein pairs, TRAM-TRIF and MAL-MyD88, ultimately activating the NF-əB pathway (Manco et al., 2010). Human and animal studies have shown LPS as a strong inducer of proinflammatory cytokines such asIL-6 and TNF in most tissues including adipocytes (Andreasen et al., 2010; Cani et al., 2007; Creely et al., 2007; Kemna et al., 2005; Stoll et al., 2004).

Overweight and obese adults have increased endotoxin exposure (Sun et al., 2010). Acute and chronic fat consumption is associated with increased exposure to endotoxin. A cross-sectional study of 201 healthy French men reported that total energy and fat, but not carbohydrate or protein were correlated with plasma LPS (Amar et al., 2008). These observations were confirmed in mice and indicated fat was more efficient in facilitating translocation of LPS into circulation than carbohydrate (Amar et al., 2008). In addition, a single high-fat meal can induce postprandial endotoxemia and inflammation (Erridge et al., 2007; Ghanim et al., 2010; Laugerette et al., 2011). Obesity-associated dysregulation of gut microbiota may also increase endotoxin exposure (Cani et al., 2007; Cani et al., 2008).

Preliminary studies in elderly individuals have demonstrated that yogurt consumption inhibits markers of endotoxin exposure in elderly individuals (Schiffrin et al., 2009). Elderly individuals (n = 23) with small-intestinal bacterial overgrowth consumed 300 g/d of yogurt with 10^9 CFU *L. johnsonii La1* for 4 wk. By the end of the trial, yogurt consumption decreased plasma levels of LBP and sCD14, LPS pattern recognition receptors in elderly with small-

intestinal bacterial overgrowth (Schiffrin et al., 2009). Furthermore, yogurt consumption also reduced plasma endotoxin in healthy elderly participants (Schiffrin et al., 2009). Small intestinal bacterial overgrowth may affect 41% of obese individuals (Jouet et al., 2011). Therefore, further studies are warranted to evaluate the ability of yogurt to reduce endotoxin exposure in obese individuals.

Mucus bilayer

The mucus bilayer is produced by goblet cells and separates gut microbiota from endothelial cells. This bilayer is formed by a mesh-like structure of mucins, high molecular weight glycoproteins with increased hydration capacity due to negative surface charges (Dharmani et al., 2009). Mucins lubricate and maintain the hydrated layer of the epithelium, as well as create a permeable unstirred, gel-like layer that facilitates nutrient exchange (Dharmani et al., 2009). The mucus bilayer is essential to the innate host defense. The outer mucus layer provides space and nutrients for the residence of commensal microflora which might inhibit the growth and invasion of pathogens; the inner layer is impervious to bacteria and acts like a protective barrier for the epithelium (Kim and Ho, 2010; Turner, 2009). The goblet cells also produce intestinal trefoil factor and resistin-like molecule-ϐ, proteins that strengthen the barrier by stabilizing the mucin polymers or regulating mucin secretions (Dharmani et al., 2009). Additionally, the mucus layer contains other defensive components such as secretory IgA and antimicrobial peptides.

Probiotics associated with yogurt may stimulate the production of intestinal mucins and improve host defense. For example, *L. plantarum* 299 v incubated with HT-29 intestinal epithelial cells increased mucin mRNA expression and inhibited the adherence of an attaching

and effecting pathogenic *E. coli. in vitro* (Mack et al., 1999). Similarly, in Wistar rats, 7 d consumption of *Lactobacilli, Bifidobacteria,* and *Streptococci* increased basal luminal mucin content by 60% (Caballero-Franco et al., 2007). Whey peptides derived from Ŭ- and ɓ- caseins also increased mucin secretion in HT29-MTX cells (Martínez-Maqueda et al., 2012). Thus, this emerging evidence suggests that dairy products or their associated probiotics could be of benefit to the mucus bilayer. A recent diet-induced obese mice model showed that obesity was associated with decreased mucus layer thickness due to the decreased level of *Akkermansia muciniphila*, a mucus layer resident that played an essential role in mucus turnover (Everard et al., 2013). Thus, it appears worthwhile to further investigate the effects of yogurt on the obese-compromised mucus layer.

Secretory IgA (sIgA)

sIgA is the major effector of the mucosa-associated lymphoid tissue (MALT) and protects against commensal bacterial penetration of the lumen (Brandtzaeg et al., 1999). MALT consists of lymphocytes such as T cells and B cells, as well as plasma cells and macrophages, which are stimulated by antigens. sIgA, dimeric or polymeric IgA, is produced by plasma cells in the intestinal mucosa and is the predominant antibody class in the intestinal lumen (Woof and Ken, 2006; Macpherson and Uhr, 2004). Interstitial sIgA inhibits pathogens and toxins by 1) preventing the adhesion and entry of pathogens and toxins by interfering with epithelial receptor recognition, 2) binding pathogens and promoting their clearance, or 3) inhibiting virus production (Corthésy, 2007). Low serum IgA may indicate compromised immune function, while high serum IgA is associated with chronic inflammation, central adiposity, and advanced age (Gonzalez-Quintela et al., 2008).

Yogurt consumption appears to modulate the gut immune function by increasing sIgA. For example, consumption of yogurt with *L. acidophilus* by 30 healthy adults increased total serum IgA and the production of specific serum IgA against an attenuated strain of *S. typhimurium* (Link-Amster et al., 1994). Consuming 400 mL yogurt with *L. acidophilus* daily for 4 wk reduced *H. pylori* and increased the serum IgA level in 38 infected children (Yang and Sheu, 2012). Rodent studies also support the IgA-promoting effects of yogurt. In a mouse model, orally administrated LAB alone and in yogurt increased the intestinal IgA producing cells and IgA (Perdigon et al., 1995). Furthermore, a 7 d yogurt treatment partially prevented the infection of *S. typhimurium* and inhibited intestinal carcinomas induced by 1-2-dimethylhydrazine (Perdigon et al., 1995). Similarly, mice fed yogurt for 4 wk had increased serum IgA after a *S. typhimurium* challenge, relative to the milk-treated control group (Puri et al., 1996). Thus, both animal and human studies have demonstrated induction of sIgA defenses following yogurt consumption, which may improve immunity.

Antimicrobial peptides

Defensins are antimicrobial peptides secreted by Paneth cells located in the crypts of the small intestinal mucosa (Porter et al., 2002). Defensins have bactericidal activity against various Gram-positive and Gram-negative bacteria (Salzman et al., 2007). These peptides facilitate bacterial membrane collapse through electrostatic and hydrophobic interactions (Zasloff, 2002). Paneth cell function and defensin levels are compromised in obese individuals, which may be explained by activated unfolded protein response in the intestine (Hodin et al., 2011). In healthy women, consumption of 200 mL yogurt with or without *B. lactis* Bb12 for 3 wk did not alter fecal ß-defensin-2, although both treatments increased fecal sIgA from baseline (Kabeerdoss et

al., 2011). However, the probiotic *Lactobacillus* and *E.coli* Nissle 1917 increased ß-defensin 2 expression in Caco-2 cells (Schlee et al., 2008; Schlee et al., 2007). Further work is needed to determine if dietary approaches are feasible to overcome obesity-compromised defensin production.

Mucosal cells and tight junctions

The innermost layer of the intestine is a monolayer of enterocytes, endocrine cells, microfold cells, G cells, and Paneth cells (Scaldaferri et al., 2012). Enterocytes are the most abundant cells and are connected by apical junctions, which are mainly adherent or tight junctions (Hartsock and Nelson, 2008). Adherent junctions consist of the transmembrane protein E-cadherin and the catenin family members, including p120-catenin, ß-catenin, and Ŭ-catenin (Hartsock and Nelson, 2008). Adherent junctions initiate and stabilize cell-cell adhesion, regulate the actin cytoskeleton, and contribute to intracellular signaling (Hartsock and Nelson, 2008). Tight junctions are composed of occludins, claudins, and junction adhesion molecules (JAM), transmembrane proteins that are linked to the cytoskeleton through zonula occludens (ZO) scaffolding proteins (Hartsock and Nelson, 2008). Tight junctions are the primary barrier to intestinal intercellular space, but are not impermeable. The paracellular pathway is selective to ions and other small molecules, and depends on the cell type (Tsukita et al., 2001).

Increased plasma endotoxin levels suggest that obese individuals have compromised intestinal barrier function (Sun et al., 2010). Compromised intestinal barrier function is proposed to contribute to chronic inflammation in obesity by initiating inflammation through endotoxin exposure (Cani et al., 2007). The perturbation of proinflammatory cytokines, gastrointestinal peptides, and endocannabinoids associated with obesity can compromise tight junctions (Bluher

et al., 2006; Cluny et al., 2012; Côté et al., 2007). In rodents, glucagon-like peptide (GLP)-2 protects barrier function, while melatonin can increase permeability (Cameron and Perdue, 2005; Cameron et al., 2003; Sommansson et al., 2013). IFN-ɔ (Bruewer et al., 2005; Clark et al., 2005; Yang et al., 2002; Youakim and Ahdieh, 1999), TNF-Ŭ(Al-Sadi et al., 2009; Li et al., 2008; Mankertz et al., 2000; Schmitz et al., 1999), and IL-6 (Al-Sadi and Ma, 2007; Yang et al., 2003) can disrupt barrier function. In contrast, IL-10 (Madsen et al., 1997; Oshima et al., 2001), transforming growth factor (TGF)-ɓ (Howe et al., 2005), and IL-17 (Kinugasa et al., 2000) improve barrier function in human T84 colonic epithelial cells. Obese ob/ob mice had improved barrier function and lower plasma LPS when treated with a CB receptor 1 antagonist (Muccioli et al., 2010).

Yogurt and its associated probiotics may improve intestinal barrier function by maintaining the expression of tight junction proteins. Yogurt with *B. lactis* prevented the increase in intestinal permeability induced by partial restraint stress in rats, and restored occludin and JAM-A expression (Agostini et al., 2012). In addition, calcium, which is rich in yogurt, plays a critical role in tight junction biogenesis and supplementation of calcium was shown to be able to inhibit alteration in tight junction function in a diabetic rat model (Leal et al., 2010; Stuart et al., 1994). Therefore, these rodent studies suggest that dairy calcium or probiotic yogurt could be beneficial for maintaining function of tight junctions.

OTHER POTENTIAL BENEFITS OF YOGURT CONSUMPTION ON GUT HEALTH

Increased yogurt consumption has the potential to improve intestinal health, ameliorate lactose intolerance, prevent constipation and diarrheal diseases, decrease allergies in vulnerable populations, and reduce the risks of colon cancer and inflammatory bowel diseases (Adolfsson et

al., 2004; Parvez et al., 2006). The mechanisms for these actions are not fully described, but may include modulating gut pH, inhibiting the proliferation and adhesion of pathogenic bacteria, secreting antibacterial substances, and regulating immune function.

Lactose intolerance

In lactase-deficient individuals, lactose enters the colon and is fermented by colonic bacteria. The colonic metabolites of lactose include short-chain fatty acids which, together with electrolytes, introduce an osmotic load that can cause diarrhea and discomfort (Lomer et al., 2008). In a cross-sectional study, subjects with self-perceived lactose intolerance had a significantly lower calcium intake from dairy foods and reported higher rate of physician-diagnosed diabetes and hypertension (Nicklas et al., 2011). Early studies indicated that subjects with lactase deficiency had better digestion and absorption of lactose from yogurt than the lactose in milk (Kolars et al., 1984). After ingestion of around 18 g of lactose in water, milk, or yogurt, subjects receiving yogurt had only one third of the hydrogen excretion, an indicator of undigested lactose, compared with those receiving lactose in water or milk (Kolars et al., 1984). Furthermore, the consumption of yogurt led to fewer symptoms of diarrhea and flatulence relative to milk (Kolars et al., 1984).

Diarrhea

Diarrhea is the leading cause of morbidity and death of children in developing countries (Boschi-Pinto et al., 2008). Emerging evidence suggests that consumption of yogurt and its related probiotic cultures prevent or treat diarrhea. In a double-blind, placebo-controlled trial, infants that received formula with *B. bifidum* and *S. thermophilus* reduced the incidence of acute diarrhea and rotavirus shedding (Saavedra et al., 1994). A meta-analysis of RCTs published from

1966 to 2000 suggested that *Lactobacillus* supplementation (10^8 to 10^{11} CFU daily) safely reduced the frequency and duration of acute infectious diarrhea in children (Van Niel et al., 2002). Moreover, a more recent meta-analysis of RCTs showed that administration of *Lactobacillus* through capsules or fermented milk during antibiotic treatment significantly reduced the risk of developing antibiotic-associated diarrhea (RR 0.35, 0.19-0.67 95% CI) (Kale-Pradhan et al., 2010). However, the risk reduction was only significant in adults after subgroup analysis (Kale-Pradhan et al., 2010).

H. pylori infection

Consumption of yogurt with *L. gasseri* for 8 wk significantly suppressed *H. pylori*-induced gastric mucosal inflammation in the elderly (Sakamoto et al., 2001). In children affected by *H. pylori,* yogurt consumption decreased serum IL-6 level after 4 wk (Yang and Sheu, 2012).

Inhibition of Colitis

The prevalence of the inflammatory bowel diseases (IBD) Crohnôs disease (CD) and ulcerative colitis (UC) is increasing in industrialized nations, and although the cause(s) are unknown, they likely result from an aberrant immune response to intestinal microbiota (Chaves et al., 2011). Probiotics administered to murine models of IBD improve disease outcomes; this has been reviewed elsewhere (Claes et al., 2011). Yogurt consumption also inhibits experimental IBD in mice. Consumption of yogurt with eight *L. bulgaricus* strains and two *S. thermophilus* strains decreased mortality rate and prevented intestinal inflammation and tissue damage in mice with trinitrobenzene sulfonic acid (TNBS)-induced intestinal inflammation (Chaves et al., 2011). Yogurt consumption prevented an increase in colonic $CD4^+$ and $CD8^+$ T cell numbers, decreased TLR-4 positive cells at 14 days, but not 3 or 7 days post TNBS administration (Chaves et al.,

2011). Yogurt without added probiotic strains inhibited TNBS-induced colitis in mice, increased the number of IgA producing cells, and decreased $CD8^+$ T cells two wk after TNBS administration (Gobbato et al., 2008).

Clinical studies have mixed outcomes for the probiotic treatment of IBD and are strain-dependent (Hedin et al., 2007; Jonkers et al., 2012; Kato et al., 2004; Lorea Baroja et al., 2007; Miele et al., 2009; Sood et al., 2009). Clinical studies have not used conventional yogurt as an intervention for IBD, despite self-reported benefits of yogurt reported by IBD patients (Cohen et al., 2013). Consumption of yogurt with *L rhamnosus* GR-1 and *L. reuteri* RC-14 improved markers of inflammation in monocytes from 20 patients with IBD, including increasing $CD4^+CD25^{high}$ T cells (Lorea Baroja et al., 2007). Yogurt could be an effective delivery vehicle for probiotic strains for treatment of IBD. However, more work is needed to identify clinically-significant probiotic strains for inhibiting colonic inflammation.

Appetite control

Obesity is a result of positive energy balance. Some studies have demonstrated that yogurt might help reduce energy intake by suppressing appetite. For example, consumption of yogurt either in semisolid or liquid form led to lower hunger and higher fullness feeling, compared with a fruit drink or dairy fruit drink (Tsuchiya et al., 2006). Similarly, subjects felt higher satiety after consumption of yogurt as evidenced by rating of hunger, appetite, desire to eat, and fullness, compared with ingestion of chocolate bars (Chapelot and Payen, 2010). Yogurt consumption also suppressed appetite rating and reduced subsequent food intake or delayed subsequent eating, compared with isovolumetric water (Dougkas et al., 2012; Douglas et al.,

2013). Therefore, yogurt consumption may provide a further benefit of appetite-suppression, although the molecular mechanisms for this effect remain uncharacterized.

CONCLUSION

Chronic inflammation is a hallmark of obesity and partially explains the increased risk of chronic disease in obese individuals. Altered gut microbiota and impaired intestinal barrier function contribute to the chronic inflammation associated with obesity. Animal models and a limited number of clinical studies demonstrate that dairy and yogurt consumption reduce chronic inflammation. New evidence from animal studies indicates that the beneficial effects of yogurt consumption might also derive from its effects on intestinal barrier function. However, there is no clinical evidence for the effects of yogurt consumption on inflammation and gut barrier function in the obese population. The benefits of yogurt for lactose intolerance are well-established, and emerging evidence supports the ability of yogurt to modulate the gut immunity and barrier function. Yogurt consumption is beneficial for intestinal health by restoring normal gut microbiota and suppressing inflammation. Further studies are needed to isolate the effects of conventional yogurt and yogurt fortified with probiotics, considering that yogurt is a vehicle for nutrients and other bioactive components. Research investigating the effects of yogurt consumption on inflammation and intestinal barrier function in the obese population may yield further insight to the mechanism(s) for its anti-inflammatory effects.

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TABLES

Table 1. Representative nutrient data bank values for plain yogurts in the U.S.[A]

Nutrient (per 6 oz)	**Whole**	**Low-fat**	**Fat-free**	**Fat-free (Greek)**
calories	104	107	95	100
total fat (g)	5.9	2.64	0.31	0.66
saturated fat (g)	3.56	1.7	0.12	0.20
MUFA (g)	1.52	0.72	0.05	0.09
PUFA (g)	0.16	0.08	0.01	0.02
cholesterol (mg)	22	10	2	8
carbohydrates (g)	7.92	11.97	13.06	6.12
sugar (g)[B]	7.92	11.97	13.06	5.51
dietary fiber (g)	0.0	0.0	0.0	0.0
protein (g)	5.9	6.77	5.73	17.32
thiamin (mg)	0.05	0.08	0.08	0.04
riboflavin (mg)	0.24	0.36	0.40	0.47
niacin (mg)	0.13	0.19	0.21	0.35
vitamin B6 (mg)	0.05	0.08	0.09	0.11
folate (mcg)	12	19	20	12
vitamin B12 (mcg)	0.63	0.95	1.04	1.28
vitamin A (RAE)	46	24	3	2
vitamin C (mg)	0.8	1.4	1.50	0.0
vitamin D (mcg)	3.0	2.0	0.0	0.0
vitamin E (mg)	0.1	0.05	0.0	0.02
vitamin K (mcg)	0.3	0.3	0.30	0.0
calcium (mg)	206	311	338	187
phosphorus (mg)	162	245	267	230
magnesium (mg)	20	29	32	19
sodium (mg)	78	119	131	61

potassium (mg)	264	398	434	240
iron (mg)	0.08	0.14	0.15	0.12
zinc (mg)	1	1.51	1.65	0.88

[A] Derived from USDA National Nutrient Database for Standard Reference, Release 26.

[B]Sweetened or fruit yogurts typically have an additional 20 g sugars per 6 oz.

Table 2. Clinical studies of yogurt on biomarkers relevant to obesity and chronic disease risk.

Category	Reference	Population	Treatment	Outcome
Lipid profiles	(Schaafsma et al., 1998)	n = 30 healthy men	375 mL/d for 3 wk, 0.5% fat, + *L. acidophilus*	Ź serum total cholesterol, Ź LDL, and Ź LDL/HLD-ratio.
	(Anderson and Gilliland, 1999)	n = 40 hypercholesterolemic individuals	200 mL/d for 4 wk, + *L. acidophilus*, unspecified fat content	Ź serum cholesterol by 3.2%
	(Kießling et al., 2002)	n = 29 women (14 hypercholesterolemic)	300 g/day for 6 mo, 3.5% fat, + *L. acidophilus* and *B. longum*	ŷ HDL
	(Fabian and Elmadfa, 2006)	n = 33 lean women	100 g/d for 2 wk and then 200 g/d for another 2 wk, 3.6% fat	Ź LDL/HLD ratio
	(Sadrzadeh-Yeganeh et al., 2010)	n = 90 lean women	300 g/d for 6 wk, 2.5% fat	Ź total cholesterol and Ź total:HDL cholesterol ratio
Inflammation	(Matsumoto et al., 2001)	n = 6 elderly (3 M, 3 F)	100 g/day for 2 wk, + *L. acidophilus* and *B. lactis*, unspecified fat content	Ź haptoglobin in feces
	(Sakamoto et al., 2001)	n = 31 elderly (29 M, 2 F)	180 g/day for 8 wk, + *L. gasseri*, unspecified fat content	Ź *H. pylori*-induced gastric mucosal inflammation
	(Schiffrin et al., 2009)	n = 36 elderly (9 M, 27	300 g/day for 4 wk, + *L.*	Ź plasma LBP, sCD14 and surrogate

		F)	*johnsonii*, unspecified fat content	markers of LPS permeability
	(Yang and Sheu, 2012)	n = 38 children	400 mL/day for 4 wk, + *L. acidophilus* and *B. lactis*, unspecified fat content	Ź serum IL-6
Appetite	(Tsuchiya et al., 2006)	n = 32 healthy men and women	acute yogurt intake (200 Kcal)	Ź hunger, ŷ fullness, ź subsequent food intake
	(Chapelot and Payen, 2010)	n = 18 lean men	acute yogurt intake (287 Kcal)	ŷ satiety, ź subsequent food intake
	(Dougkas et al., 2012)	n = 40 overweight men	acute yogurt intake (201 Kcal)	Ź appetite, Ź subsequent energy intake
	(Douglas et al., 2013)	n = 15 women	acute yogurt intake (160 Kcal)	Ź hunger, ŷ fullness, and delayed subsequent eating

Table 3. Obesity-related changes in biomarkers of inflammation.

Reference	Samples	Population	Markers
(Hotamisligil et al., 1995)	adipose tissue	premenopausal women, n = 18 lean/n = 19 obese	ŷ TNF-ŭmRNA; body weight reduction Ź TNF-ŭ mRNA
(Kern et al., 2001)	adipose tissue	n = 50 lean/n = 50 obese	ŷ TNF-ŭsecretion
	plasma		ŷ IL-6
(Panagiotakos et al., 2005)	serum	3042 adults	ŷ CRP, ŷ TNF-ŭ, ŷ amyloid A, ŷ IL-6 in subjects with central adiposity
(Kim et al., 2006)	serum	50 obese and 50 lean adults	ŷ MCP-1, ŷ IL-8 and ŷ CRP
(Herder et al., 2007)	serum	519 adolescents	IL-6, IL-18 and interferon-ɔ-inducible protein-10 positively associated with BMI and waist circumference
(Mauras et al., 2010)	plasma	203 children	ŷ hsCRP, ŷ fibrinogen, ŷ IL-6 and ŷ plasminogen activator inhibitor-1
(Brake et al., 2006)	adipose tissue	High-fat-fed male mice	ŷ ICAM-I, ŷ IL-6 and ŷ MCP-1 mRNA
(Ehses et al., 2007)	pancreatic islets	High-fat-fed mice	ŷ IL-6, ŷ IL-8 and ŷ macrophage inflammatory protein 1ŭ
(De Souza et al., 2005)	hypothalamus	High-fat-fed rats	ŷ TNF-ŭ, ŷ IL-1ɓ, and ŷ IL-6