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Effects of Goat Milk Yogurt Supplemented with Citrus Concentrate on Blood Glucose and Serum Lipids in Diabetic Rats

Jun-Sang Ham, Ji-Hye Shin, Aera Jang, Seok-Geun Jeong, Kwang-Wook Park[1], Hyun-Uk Kim[1], Su Yeon Kang[2], Hye Joong Hwang[2], and Wan Kyu Lee[2,*]
National Institute of Animal Science, RDA, Suwon 441-706, Korea
[1]Life Science Institute, MGEN Inc., Seoul 153-023, Korea
[2]College of Veterinary Medicine, Chungbuk National University, Cheongju 361-763, Korea

밀감농축액 첨가 산양발효유가 당뇨병 유발 랫드의 혈당 및 혈액지질에 미치는 영향

함준상 · 신지혜 · 장애라 · 정석근 · 박광욱[1] · 김현욱[1] · 강수연[2] · 황혜중[2] · 이완규[2,*]
축산과학원 축산생명환경부, [1](주)엠젠 생명과학연구소, [2]충북대학교 수의과대학

Abstract

The effects of fermented goat milk supplemented with citrus concentrate on blood glucose levels in streptozotocin–nicotinamide-induced diabetic rats were examined. Streptozotocin-nicotinamide-induced diabetic rats (type II) were divided into five experimental groups treated with metformin, goat milk, fermented goat milk, fermented goat milk containing citrus concentrate, or no supplementation (control). The rats in each group were examined weekly for blood levels of glucose, total cholesterol, triglyceride, HDL-cholesterol, LDL-cholesterol, and body weight. On the 24^{th} day of the experiment, an oral glucose tolerance test (OGTT) was carried out. Administration of fermented goat milk to the diabetic rats significantly decreased blood glucose and triglyceride levels, while administration of metformin (33.3 mg/kg body weight) did not significantly lower blood glucose levels. Fermented goat milk containing citrus concentrate caused a significant decrease in blood glucose levels in the OGTT at 30 min. This study shows that supplementation with fermented goat milk containing citrus concentrate may be a practical method of reducing blood glucose levels in type II diabetics.

Key words: fermented goat milk, diabetes, citrus, blood glucose levels

Introduction

Goat milk and its products such as yogurt, cheese, and infant formula, have attracted increasing attention because of their hypoallergenic nature and their nutritional value to starving and malnourished people in the developing world (Haenlein, 2004). Although the composition of goat milk is similar to that of cow's milk, goat milk products are claimed to be superior in terms of hypoallergenicity, fat morphology, and fatty acid composition (McCullough, 2005). Moreover, the health-promoting nature of yogurt and probiotic bacteria has been widely publicized. Reported nutritional and health-promoting attributes of yogurt include the prevention and treatment of diarrhea, induction of protective immunity against pathogens and tumors, prevention of allergies, modulation of gastrointestinal function, and alleviation of lactose intolerance and hypertension (McKinley, 2005). Recently, Yadav *et al.* (2007) reported that a probiotic dahi-supplemented diet significantly delayed the onset of glucose intolerance, hyperglycemia, hyperinsulinemia, dyslipidemia, and oxidative stress in high fructose-induced diabetic rats, with the implication of reducing the risk of diabetes and its complications.

Diabetes mellitus (DM) is a metabolic disorder characterized by hyperglycemia and abnormalities of carbohydrate, protein, and fat metabolism, leading to hyperglycemia. Complications of DM include hyperlipidemia, hyperinsulinemia, hypertension, and atherosclerosis (American Dia-

*Corresponding author : Wan Kyu Lee, Chungbuk National University, Cheongju 361-763, Korea. Tel: 82-43-261-2960, Fax: 82-43-267-3150; E-mail: wklee@cbu.ac.kr

betes Association, 2002). DM affects approximately 5% of the world's population and more than 300 million people may suffer from diabetes by the year 2025 (King *et al.*, 1998). More than 95% of patients with DM have type II (T2DM). Measures for combating T2DM include adjusting eating habits, increasing physical activity, and taking certain medications. The oral medications commonly used include the sulfonylureas, which stimulate the pancreas to make more insulin, metformin and/or glitazones, which improve insulin resistance, and alpha-glucosidase inhibitors, which decrease sugar absorption (Park *et al.*, 2003). However, these oral medications cause various side effects, such as low blood glucose levels, increased body weight, hepatotoxicity, and high blood lactate (Park *et al.*, 2003). Thus, attempts to find natural substances that can replace these medications to control blood glucose levels are continuing.

Plant flavonoids, when consumed in large amounts, have been reported to have antioxidant, mild estrogenic, and hypolipidemic activities (Choi *et al.*, 1991; Bhathena and Velasquez, 2002). Among naturally occurring flavonoids, hesperidin and naringin have been shown to have no side effects, and humans have been eating grapes and citrus fruits throughout history (Choe *et al.*, 2001). Recently, the lipid-lowering effects and antioxidant capacity of flavonoids were also demonstrated when 400 mg naringin/day was given to subjects with hypercholesterolemia for 8 wk (Jung *et al.*, 2003). Additionally, several flavonoids have been shown to exert effects on glucose transport, insulin-receptor function, and peroxisome proliferators-activated receptor (PPAR) activation, all of which play roles in alleviating diabetes (Shisheva and Shechter, 1992; Liang *et al.*, 2001; Song *et al.*, 2002). In addition, citrus concentrate incorporated into goat milk yogurt has been reported to reduce its typical "goaty" flavor (Ham *et al.*, 2007).

In this study, we examined the effects of goat milk yogurts containing citrus concentrate on blood glucose levels and serum lipid profiles in streptozotocin–nicotinamide-induced type-II diabetic rats.

Materials and Methods

Experimental animals and diets

Healthy male albino Wistar rats (200±10 g body weight) were obtained from Central Laboratory Animals, Inc. (Seoul, Korea). The rats were fed with a standard laboratory diet (Table 1) (American Institute of Nutrition, 1977) and were provided water *ad libitum*. The rats were maintained in stainless cages (3 rats/cage) and kept on a 12/12-h, light-dark cycle. Temperature and humidity were kept at 25±2°C and 60±5%, respectively. Type II diabetes was induced in overnight-fasted rats by a single intraperitoneal (i.p.) injection of 65 mg/kg streptozotocin (Sigma-Aldrich Co., St. Louis, MO, USA), followed by the i.p. administration of 120 mg/kg of nicotinamide (Sigma-Aldrich Co.) 15 min later (Masiello et al., 1998). Streptozotocin was dissolved in citrate buffer (pH 4.5) and nicotinamide was dissolved in normal 0.9% saline. Hyperglycemia was confirmed by elevated blood glucose levels measured at 72 hr and again on the seventh day after the injection. The hyperglycemic diabetic rats were then used in this study (ADA, 1998; Masiello *et al.*, 1998; Shirwaikar *et al.*, 2005; Nakamura *et al.*, 2007). Goat milk and goat milk fermented by a commercial starter containing *Lactobacillus acidophilus*, *L. bulgaricus*, and *Streptococcus thermophilus* (plain yogurt) were obtained from MGEN (Seoul, Korea).

Table 1. Composition of experimental diet fed to rats (per 100 g)

Moisture (g)	11.39
Protein (g)	22.12
Fat (g)	6.33
Ash (g)	6.85
Fiber (g)	3.04
Nitrogen free extract (g)	50.28
Calories (kcal)	347
Starch (g)	38.50
Sugar (g)	4.19

Experimental design

The diabetic rats were randomly divided into five groups (n = 7 each). Rats in each group, including the control group (n = 7), were fed with a standard laboratory diet for 4 wk, during which time the DR group received sterilized water (3.3 g/kg of body weight), the DM group received metformin–HCl (33.3 mg/kg of body weight; Daewoong, Seoul, Korea), the DGM group received goat milk (3.3 g/kg of body weight; MGEN), the DGY group received fermented goat milk (3.3 g/kg of body weight; MGEN), the DGTC group received fermented goat milk containing 2% citrus concentrates (3.3 g/kg of body weight; French Korean Aromatics, Yongin, Korea), and the normal control (NR) group received sterilized water (3.3 g/kg of body weight) every day. The body weight of the rats was measured weekly, and blood samples were taken from the cephalic vein every week after overnight fasting. The oral glucose tolerance test was performed on overnight-fasted animals. After glucose (2 g/kg of body weight) administration, blood samples for the OGTT were withdrawn from the cephalic vein under ether inhalation at 0, 30, 60, and 120 min.

Blood analysis

The glucose, total cholesterol, triglyceride, HDL, and LDL contents of the blood samples were assayed using the Automatic Chemistry Analyzer System (BioSed, Rome, Italy) in the Laboratory of Clinical Pathology at Chungbuk National University. The fasting blood glucose levels in the OGTT were estimated using an Accu-Chek Go Kit (Roche Diagnostic GmbH, Mannheim, Germany).

Statistical analysis

The collected data were analyzed using the Statistical Package for the Social Sciences software (SPSS Inc., Chicago, IL, USA). Significant differences among the groups were determined by a one-way ANOVA. Duncan's multiple-range test was performed if differences were identified between the groups at $p<0.05$.

Results and Discussion

Body weight

The body weight changes in rats fed with goat milk, fermented goat milk, and fermented goat milk containing citrus concentrates are shown in Table 2. Rats in the NR and DGYC groups gained more body weight than the DGM group rats. The same trend was observed after 3 wk and 4 wk, although no significant difference was found thereafter. The antidiabetic drug metformin showed no noticeable effect on body weight in the diabetic rats.

Blood glucose

The effects of goat milk, fermented goat milk, and fermented goat milk containing citrus concentrates on blood glucose levels are shown in Table 3. Blood glucose levels of normal rats and diabetic rats after 4 wk were 116.3 and 252.6 mg/dL, respectively. While not statistically significant, metformin and goat milk did reduce blood glucose levels to 171.4 and 212.9 mg/dL, respectively. However, fermented goat milk and fermented goat milk containing citrus concentrate significantly ($p<0.05$) lowered blood glucose to 121.7 and 132.9 mg/dL, respectively. On the initial day of the experiment, no significant difference was found among the diabetic groups, but statistically significant changes were observed throughout the experimental period. After 4 wk, the blood glucose levels of DGY and DGYC group rats were significantly lower than those of diabetic rats, while no difference was found in blood glucose levels between DM and

Table 2. Body weights of the experimental rats

Group	Time (wk)				
	0	1	2	3	4
NR	293.5±11.6	325.6±13.8	343.5±20.3^{a}	333.1±21.2	351.9±21.1
DR	275.4±23.5	294.5±31.9	305.5±38.8^{ab}	289.1±46.6	308.8±46.7
DM	280.7±23.5	303.2±31.0	322.7±36.9^{ab}	311.8±40.0	327.5±37.8
DGM	272.1±30.4	293.0±41.8	293.1±59.4^{b}	290.7±54.2	309.6±54.4
DGY	284.5±12.3	305.3±18.4	324.2±24.6^{ab}	315.8±25.8	334.4±28.2
DGYC	295.4±19.2	325.1±23.7	338.8±24.1^{a}	327.4±18.7	347.5±20.9

Data are expressed as means±SD.
$^{a-c}$ Values with different superscripts in the same column differ significantly ($p<0.05$).
NR, normal rats; DR, diabetic rats; DM, diabetic rats fed with metformin; DGM, diabetic rats fed with goat milk; DGY, diabetic rats fed with fermented goat milk yogurt; DGYC, diabetic rats fed with fermented goat milk with citrus concentrates.

Table 3. Blood glucose levels in the experimental rats

Group	Time (wk)				
	0	1	2	3	4
NR	104.7± 17.0	141.9± 21.0^{b}	135.0± 11.7^{b}	122.0± 19.1^{b}	116.3± 14.5^{b}
DR	246.7±149.8	269.0±133.0^{a}	261.1±145.1^{a}	274.1±141.8^{a}	252.6±144.1^{a}
DM	248.9±141.8	153.3± 48.7^{b}	189.4± 76.2^{abc}	179.9± 85.6^{ab}	171.4± 83.2^{ab}
DGM	254.7±133.1	201.9±109.0^{ab}	239.3±132.8^{ab}	226.0±135.7^{ab}	212.9±135.8^{ab}
DGY	247.9±129.3	151.4± 20.9^{b}	129.7± 12.8^{b}	129.7± 15.1^{b}	121.7± 12.6^{b}
DGYC	244.9±128.6	165.3± 20.2^{b}	148.7± 13.2^{ab}	127.7± 9.0^{b}	132.9± 15.1^{b}

Data are expressed as means±SD
$^{a-c}$ Values with different superscripts in the same column differ significantly ($p<0.05$).
NR, normal rats; DR, diabetic rats; DM, diabetic rats fed with metformin; DGM, diabetic rats fed with goat milk; DGY, diabetic rats fed with fermented goat milk yogurt; DGYC, diabetic rats fed with fermented goat milk with citrus concentrates.

DGM group rats. Fermented goat milk apparently reduced blood glucose levels more than the antidiabetic drug metformin. Tabuchi *et al.* (2003) reported that glucose intolerance and hyperglycemia were significantly delayed by feeding with *Lactobacillus* GG during the progression of streptozotocin-induced diabetes in rats. Yadav *et al.,* (2007) stated that dietary dahi (yogurt) may play a role in slowing the biochemical changes that lead to diabetes.

Serum triglycerides

Diabetic rats given no supplements showed higher blood triglyceride levels than those of the other rats at 0, 3, and 4 wk (Table 4). After 3 and 4 wk of supplementation with fermented goat milk, with or without citrus concentrate, the triglyceride levels in the blood of the experimental rats were significantly decreased ($p<0.05$). Jung *et al.* (2006) reported the plasma triglyceride and total cholesterol concentrations were also significantly lower in the blood of rats fed hesperidin- and naringin-supplemented diets. Furthermore, although the plasma HDL-cholesterol concentrations did not differ among the groups, the ratio of HDL-cholesterol to total cholesterol was significantly higher in the groups fed diets supplemented with hesperidin and naringin.

Blood cholesterol

The effects of goat milk, fermented goat milk, and fermented goat milk supplemented with citrus concentrates on total blood cholesterol levels in diabetic rats are shown in Table 5. Total blood cholesterol contents were not significantly affected by diet or supplementation. Additionally, the diabetic drug metformin showed no significant effects on serum cholesterol levels in diabetic rats. However, supplementation with fermented goat milk, with (DGYC) or without (DGY) citrus concentrate, increased the serum HDL levels in diabetic rats after 2 and 4 wk, although goat milk (DGM) alone decreased serum HDL levels after 4 wk (Table 6). Liong and Shah (2006) reported that a diet containing *L. casei* ASCC 292, fructo-oligosaccharide, and maltodextrin lowered total serum cholesterol and triglyceride levels, and a diet containing *L. casei* ASCC 292 and maltodextrin increased serum HDL-cholesterol levels. Other symbiotic diets showed a tendency to increase serum HDL-cholesterol, however rats receiving symbiotic diets did not show any changes in LDL-cholesterol levels compared to rats on a control diet (Liong and Shah, 2006). In this study, the LDL-cholesterol levels after 4 wk were not significantly affected by diet or supplementation (Table 7).

Table 4. Blood triglyceride levels in the experimental rats

Group	Time (wk)				
	0	1	2	3	4
NR	47.5±17.5[c]	29.7±10.9	35.4±14.8	40.1± 15.3[ab]	44.5±21.7[b]
DR	142.6±86.2[a]	62.3±64.0	61.9±47.0	116.1±146.1[a]	81.1±54.1[a]
DM	83.3±13.5[bc]	42.9± 8.8	53.6±25.2	43.2± 38.2[ab]	44.7±14.7[b]
DGM	110.0±50.6[ab]	48.0±25.6	53.0±18.6	52.4± 40.6[ab]	47.0±38.8[b]
DGY	100.5±38.6[ab]	35.8± 5.6	52.7±15.6	32.0± 5.1[b]	38.1±18.0[b]
DGYC	102.4±52.0[ab]	33.9±13.1	50.7±15.1	37.1± 13.6[b]	28.8± 6.3[b]

Data are expressed as means±SD

[a-c] Values with different superscripts in the same column differ significantly ($p<0.05$).

NR, normal rats; DR, diabetic rats; DM, diabetic rats fed with metformin; DGM, diabetic rats fed with goat milk; DGY, diabetic rats fed with fermented goat milk yogurt; DGYC, diabetic rats fed with fermented goat milk with citrus concentrates.

Table 5. Total blood cholesterol levels in the experimental rats

Group	Time (wk)				
	0	1	2	3	4
NR	75.3± 7.4	71.4± 8.9	74.3± 8.3	70.9± 8.7	61.9± 6.3
DR	77.1±11.7	69.0±12.8	72.7±11.7	86.3±40.7	65.1±11.1
DM	75.3± 9.7	69.3±10.4	75.0± 9.7	69.7± 7.4	61.9± 8.7
DGM	73.3± 8.9	69.4± 7.6	74.1± 8.0	78.3±13.3	62.3± 9.3
DGY	78.6± 9.6	75.4± 6.2	77.0± 5.5	73.7± 5.4	67.4± 7.8
DGYC	71.4± 6.1	75.9±10.3	77.0±10.1	75.9± 8.7	64.6± 7.7

Data are expressed as means±SD

NR, normal rats; DR, diabetic rats; DM, diabetic rats fed with metformin; DGM, diabetic rats fed with goat milk; DGY, diabetic rats fed with fermented goat milk yogurt; DGYC, diabetic rats fed with fermented goat milk with citrus concentrates.

Table 6. Blood HDL cholesterol levels in the experimental rats

Group	Time (wk)				
	0	1	2	3	4
NR	31.7±2.1	27.9±2.0	24.1±1.8[b]	27.1± 2.5	23.9±2.4[b]
DR	33.0±5.0	27.0±4.2	23.4±3.4[b]	30.4±11.5	21.9±2.9[ab]
DM	32.1±3.3	26.3±1.9	23.9±2.6[b]	26.0± 1.5	20.3±2.1[c]
DGM	34.9±9.5	26.4±1.5	24.4±2.6[b]	28.1± 3.7	20.6±2.4[c]
DGY	32.7±3.9	27.3±2.0	30.1±0.7[a]	31.0± 2.0	28.4±2.0[a]
DGYC	32.0±3.0	27.6±2.8	30.0±2.2[a]	29.7± 2.0	27.3±1.5[a]

Data are expressed as means±SD

[a-c] *Values with different superscripts in the same column differ significantly (p<0.05).*

NR, normal rats; DR, diabetic rats; DM, diabetic rats fed with metformin; DGM, diabetic rats fed with goat milk; DGY, diabetic rats fed with fermented goat milk yogurt; DGYC, diabetic rats fed with fermented goat milk with citrus concentrates.

Table 7. Blood LDL levels in the experimental rats

Group	Time (wk)				
	0	1	2	3	4
NR	34.1±4.7[a]	37.6±6.9[ab]	43.1± 7.3	35.7± 6.6	29.1±4.5
DR	19.8±6.3[b]	29.5±8.3[b]	36.9±10.2	32.6±13.4	27.1±9.2
DM	26.5±8.3[ab]	34.4±9.2[ab]	40.4± 9.5	35.1± 4.8	32.6±6.8
DGM	21.5±8.1[b]	33.4±3.9[ab]	39.1± 6.6	39.7± 5.0	32.3±6.4
DGY	25.8±5.4[ab]	41.0±6.0[a]	36.3± 4.8	36.3± 4.1	31.4±7.2
DGYC	23.3±9.3[b]	41.5±7.6[a]	36.9± 9.0	38.7± 7.1	31.5±5.8

Data are expressed as means±SD

[a-c] Values with different superscripts in the same column differ significantly (p<0.05).

NR, normal rats; DR, diabetic rats; DM, diabetic rats fed with metformin; DGM, diabetic rats fed with goat milk; DGY, diabetic rats fed with fermented goat milk yogurt; DGYC, diabetic rats fed with fermented goat milk with citrus concentrates.

Table 8. Oral glucose tolerance in the experimental rats

Group	Time (min)			
	0	30	60	120
NR	105.1± 13.7[b]	142.6± 11.7[b]	129.7± 8.3[c]	113.0± 15.1[c]
DR	223.3± 94.2[a]	320.7±116.7[a]	311.6±132.9[a]	267.9±109.9[a]
DM	168.1± 75.5[ab]	215.6± 95.6[ab]	178.7± 83.5[bc]	166.1± 77.7[bc]
DGM	208.3±108.7[a]	242.1±139.4[ab]	262.0±158.9[ab]	236.9±130.4[ab]
DGY	141.6± 47.3[ab]	233.1± 82.6[ab]	231.4± 69.6[abc]	213.3± 64.9[ab]
DGYC	111.0± 14.0[b]	199.3± 50.6[b]	199.9± 52.7[abc]	180.1± 41.9 [abc]

Data are expressed as means±SD

[a-c] Values with different superscripts in the same column differ significantly (p<0.05).

NR, normal rats; DR, diabetic rats; DM, diabetic rats fed with metformin; DGM, diabetic rats fed with goat milk; DGY, diabetic rats fed with fermented goat milk yogurt; DGYC, diabetic rats fed with fermented goat milk with citrus concentrates.

Oral glucose tolerance

Oral glucose tolerance changes in diabetic rats were determined over 120 min. Fermented goat milk with citrus concentrate reduced glucose tolerance significantly, reaching the same level as normal rats (p<0.05) within 30 min. However, goat milk and fermented goat milk did not seem to affect the glucose tolerance of the diabetic rats. Thus, supplementation of the fermented goat milk with citrus concentrate showed a significant decrease in oral glucose tolerance in diabetic rats within 30 min.

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