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Health-promoting effects of bovine colostrum in Type 2 diabetic patients can reduce blood glucose, cholesterol, triglyceride and ketones☆

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Abstract

Bovine colostrum (BC) has been reported to enhance immune function, reduce fat accumulation and facilitate the movement of glucose to the muscle. However, very few attempts have been made to examine its anti-diabetic effects in diabetes patients. The aim of this study was to evaluate whether BC decreases blood glucose, as well as cholesterol, triglyceride (TG) and ketones levels, which can be elevated by obesity and stress in Type 2 diabetic patients. Sixteen patients (men=8, women=8) with Type 2 diabetes were randomized into the study. Each ingested 5 g of BC on an empty stomach every morning and night for 4 weeks. Blood glucose, ketones (β-hydroxybutyric acid), total cholesterol and TGs were measured every week. In both the men and women, blood glucose levels at 2 and 8 h postprandial decreased continually during the experimental period. The rate of decrease in blood glucose at 8 h postprandial was not different between the men and women, but was higher in the women (14.25±2.66) than in the men (10.96±1.82%) at 2 h postprandial. Total cholesterol and TG levels decreased significantly in both the men and women after 4 weeks. Also, β-hydroxybutyric acid level decreased with BC ingestion, but this was not significant. These results suggest that BC can decrease levels of blood glucose and ketones, as well as reduce cholesterol and TGs, all of which may cause complications in Type 2 diabetic patients.

Keywords: Bovine colostrum; Blood glucose; Cholesterol; Triglyceride; Ketone; Type 2 diabetes

1. Introduction

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action or both. Type 2 diabetes (non–insulin-dependent diabetes mellitus), the most prevalent form of the disease, is caused by a complicated interplay of genes, environment, lifestyle choices, insulin abnormalities, increased glucose production in the liver, increased fat breakdown and possibly defective hormonal secretions in the intestine [1]. The recent dramatic increase in diabetes indicates that lifestyle factors (obesity and sedentary lifestyle) are particularly important in triggering the genetic elements that cause this type of diabetes. In fact, many studies have shown that diet and exercise slow the onset of diabetes in persons with impaired glucose tolerance [2,3].

Overall, individuals with Type 2 diabetes mellitus are two to four times more likely to suffer from cardiovascular diseases (CVD) than nondiabetic individuals [4]. Disorders in high-density lipoprotein cholesterol and triglycerides (TGs) could be key CVD risk factors in patients with Type 2 diabetes [5,6]. A low level of high-density lipoprotein cholesterol is common in patients with diabetes mellitus and is a primary determinant of CVD risk, independent of the level of low-density lipoprotein cholesterol. Moreover, increased levels of very

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low density lipoprotein cholesterol and TGs can be associated with endothelial dysfunction, impaired microcirculatory flow and increased thrombotic risk [7].

Bovine colostrum (BC) is the pre-milk fluid produced from a cow's mammary glands during the first few days after birth. It is a rich source of antibodies, growth factors and nutrients for the suckling neonate and may provide passive immunity to the newborns against various infectious microorganisms. Although various studies on the beneficial effects of colostrum have been performed, there are few reports on its anti-diabetic effects. Indeed, many studies have confirmed the presence of insulin-like growth factor-1 (IGF-1) in BC [8–10] and indicated concentrations of IGF-1 and IGF-11 in the first colostrum that range from 289 to 902 pg/L. IGF-1 is suggested to have beneficial effects on glucose homeostasis since it lowers blood glucose and increases insulin sensitivity [11]. It was reported that IGF-1 levels are generally lower in Type 2 diabetic patients, and the progressive age-dependent decline of IGF-1 is higher in Type 2 diabetic patients than in healthy individuals [12,13]. Furthermore, leptin in BC, which works in concert with IGF-1, could be beneficial to people with elevated cholesterol and TG levels, because it is linked to fat breakdown in muscle. Interestingly, Type 2 diabetic patients were shown to have significantly lower leptin levels compared to nondiabetic subjects after controlling for age and percent body fat [14,15].

In the present study, we evaluated whether BC can decrease blood glucose level, as well as reduce levels of cholesterol and TG, which can be elevated by obesity and stress in Type 2 diabetic patients. In addition, by testing ketone levels, which are produced by the liver in large amounts as a result of Type 1 diabetes, we selected patients in the early and middle stages of Type 2 diabetes and then investigated ketone levels in these Type 2 diabetic patients after feeding BC.

2. Subjects and methods

2.1. Subjects

Sixteen subjects (men=8, women=8) who signed informed consent forms were randomized into a clinical study. Inclusion criteria included (1) being 35–65 years of age, (2) regularly consuming three meals daily, (3) having Type 2 diabetes as evidenced by taking antihyperglycemic agents, (4) total cholesterol level of 150-300 mg/dl, (5) TG level of 70-600 mg/dl, (6) ketone level (*β*-hydroxybutyrate) of <0.6 mmol/L and (7) no experimentation with diet and drinking within the last 3 months. Exclusion criteria included pregnancy, nursing subjects and smokers. The study was performed under conditions that did not change the patient's lifestyle. Table 1 shows the baseline characteristics of the subjects who were deemed eligible according to the study protocol.

Table 1
Baseline subject characteristics

Parameter	A	B	C	D	E	F	G	H	Mean±S.E.M.
Men [a]									
Age (years)	48	49	54	59	40	36	60	60	50.75±3.04
Height (cm)	167	170	163	163	171	167	173	161	166.88±1.42
Weight (kg)	79	55	65	60	65	80	58	60	65.25±3.11
Women [a]									
Age (years)	45	55	56	49	51	58	40	40	49.25±2.33
Height (cm)	156	162	153	155	155	156	156	161	156.75±1.03
Weight (kg)	65	58	51	48	64	51	66	80	60.38±3.50

[a] The individual subjects are represented as A–H. All subjects were Korean.

2.2. Procedures and product

The clinical demonstration period was 4 weeks. The subjects ingested 5 g of BC powder (Immuno-Dynamics, Inc., Fennimore, WI) on an empty stomach (8 h postprandial) every morning and night. In the previous animal study using the same BC samples, the feeding of diet consisting equivalent amount of BC significantly reduced blood glucose levels and excretions of urea and creatinine in diabetic rats [16]. The BC powder was pasteurized under the production outline USDA license 3606:00, a proprietary method during processing. Then, microbiological analysis was performed before the BC was stored at −50°C for subsequent analysis. The nutrient composition of the BC is shown in Table 2. In preparation for the treatment, the subjects (1) kept meals under 1500 kcal from 1 week prior until the end of the study, (2) avoided taking their antihyperglycemic agents and eating health- and diet-related foods, and (3) refrained from special exercise.

2.3. Measurements

In order to measure the relative nutritional value of BC used in this study, the change in casein, albumin, total protein, fat and lactose concentrations of BC according to the time after calving was measured.

In all subjects with Type 2 diabetes, the following parameters were measured every week: blood glucose (2 and 8 h postprandial), total cholesterol, TGs and ketones (*β*-hydroxybutyric acid). Blood glucose, total cholesterol and TG values were measured with Accutrend GCT (Roche Diagnostics, Mannheim, Germany) based on the reflectance photometric method. β-Hydroxybutyric acid was determined using Optium Xceed (Abbott Diabetes Care, Doncaster, Australia) based on the electrochemical method. Whole blood was used for all measurements and was collected by finger prick in all subjects every morning on an empty stomach (except for the 2 h postprandial blood glucose) and analyzed immediately afterwards. For the measurements using the Accutrend GCT and Optium Xceed, blood samples of 10–30 and 5 μl were taken, respectively.

2.4. Statistical analysis

Statistical differences were determined by ANOVA, with mean separations performed by Duncan's multiple range tests using the general linear model procedure of the SAS statistical software package [17]. Whole blood samples

Table 2
Nutrient composition of BC

Constituents	%
Protein	56.60
Fat	19.50
Lactose	12.00
IgG	26.00 (45.90% of protein)
Total immunoglobulin	31.20 (55.10% of protein)
Constituents	**μg/g**
IGF-1 [a]	4.10
Leptin	0.14
Ecos lactoferrin	6400.00
Thymosin alpha 1	105.10
Thymosin beta 4	2500.00

[a] Insulin-like growth factor Type 1.

were used for analysis, and the variation between samples (n=8) is expressed as the pooled S.E.M. or mean±S.E.M., where applicable.

3. Results

3.1. Change in casein, albumin, total protein, fat and lactose concentrations of BC according to the time after calving

The concentration of albumin and total protein of BC was higher in the earlier stages of post-calving, and that of fat and lactose was lower (Fig. 1). The casein concentration of BC at 0 and 6 h after calving was relatively lower, but it was not significant (P>.05). The BC that was used in the following studies was obtained at 6 h post-calving.

3.2. Effects of BC on blood glucose in Type 2 diabetic patients

In the present study, BC decreased blood glucose levels (2 and 8 h postprandial) continually in Type 2 diabetic patients (both men and women) during the experimental period (Table 3). The rate of decrease in blood glucose at 8 h postprandial was not different between the men and women, but the rate of decrease at 2 h postprandial was higher in women (14.25±2.66%) than in men (10.96±1.82%) after 4 weeks.

As a whole, the rate of decrease in blood glucose by BC was highest among the subjects with relatively high glucose levels within a test group (men: 8 h postprandial, B=25.75%; women: 8 h postprandial, A=17.69%; women: 2 h postprandial, F=26.50%).

3.3. Effects of BC on total cholesterol, TGs and ketones in Type 2 diabetic patients

Levels of total cholesterol and TGs, in both the men and women with Type 2 diabetes, decreased significantly with BC administration (Table 4). The rate of decrease in TGs for the women during the test period was nearly double that of the men, but it was not for total cholesterol. In addition, β-hydroxybutyric acid was significantly decreased in both men and women by BC treatment.

4. Discussion

The efficacy of BC on Type 2 diabetic patients was studied in the present study. The results demonstrated that BC could effectively decrease the levels of blood glucose and ketone bodies, as well as reduce the levels of cholesterol and TG, which can be elevated by obesity and stress in Type 2 diabetic patients.

Microalbuminuria in Type 2 diabetes is a powerful independent predictor of all-cause mortality, cardiovascular mortality and morbidity, including stroke, myocardial infarction, congestive heart failure and progressive renal failure [18]. In addition, in a study on blood glucose and plasma insulin responses to test milk samples in healthy normal volunteers, Salminen et al. [19] reported that fat-free milk, especially low-lactose fat-free milk, was proved to be suitable as diabetic diets. The BC that was used in this study was obtained within 6 h post-calving, and it was confirmed that our BC samples contained high protein (especially albumin), low fat and lactose. Therefore, BC that was obtained in earlier stages of post-calving could be more beneficial to Type 2 diabetic patients compared with BC in later stage of post-calving.

People with poorly controlled blood glucose levels are more likely to have clinical complications of diabetes, such as CVDs, blindness and kidney damage. Many aspects of these complications can be limited, and even prevented in some instances, with early management of the condition, including the effective control of blood glucose levels. In the present study, BC decreased blood glucose levels (2 and 8 h postprandial) continually in Type 2 diabetic patients (both men and women) for 4 weeks, and the rate of decrease at 2 h postprandial was higher in the women than in the men after 4 weeks. Compared to human colostrum, BC contains much higher concentrations of IGF-1, which has beneficial effects on glucose homeostasis. Although several adverse effects caused by the administration of IGF-1 to Type 2 diabetic

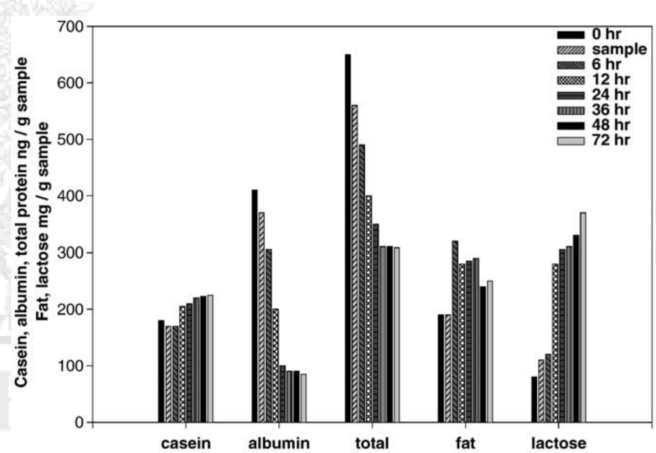

Fig. 1. Change in casein, albumin, total protein, fat and lactose concentration of BC according to the time after calving.

Table 3
Effects of BC on blood glucose in Type 2 diabetic patients

	Blood glucose levels (mg/L)								Mean±S.E.M.
	A	B	C	D	E	F	G	H	
Men [a]									
8 h after a meal									
Baseline	111	167	112	113	127	110	119	100	119.88±6.79
1 week	108	135	120	110	107	113	109	99	112.63±3.56
2 weeks	109	133	108	108	105	109	110	100	110.25±3.22
3 weeks	106	133	95	99	105	105	111	89	105.38±4.35
4 weeks	105	124	97	106	101	104	110	90	104.63±3.29
Decrease (%) [b]	5.41	25.75	13.39	6.19	20.47	5.45	7.56	10.00	11.78±2.52
2 h after a meal									
Baseline	149	272	183	167	177	210	171	156	185.63±13.05
1 week	142	265	196	159	155	201	159	154	178.88±13.42
2 weeks	145	257	167	147	150	196	157	154	171.63±12.63
3 weeks	139	255	155	145	155	195	158	128	166.25±13.50
4 weeks	139	258	144	150	147	195	155	139	165.88±13.68
Decrease (%)	6.71	5.15	21.31	10.18	16.95	7.14	9.36	10.90	10.96±1.82
Women [a]									
8 h after a meal									
Baseline	130	123	107	115	119	118	118	120	118.75±2.16
1 week	125	117	87	102	112	106	112	113	109.25±3.74
2 weeks	115	115	90	101	114	109	113	116	109.13±3.03
3 weeks	105	112	95	102	109	105	108	109	105.63±1.75
4 weeks	107	110	95	100	105	107	110	103	104.63±1.70
Decrease (%)	17.69	10.57	11.21	13.04	11.76	9.32	6.78	14.17	11.82±1.08
2 h after a meal									
Baseline	198	160	144	162	182	234	200	281	195.13±14.80
1 week	198	159	131	151	176	165	198	250	178.50±12.15
2 weeks	188	154	133	153	172	172	200	250	177.75±11.90
3 weeks	171	155	130	149	159	178	201	227	171.25±10.19
4 weeks	178	149	135	150	152	172	169	211	164.50±7.80
Decrease (%)	10.10	6.88	6.25	7.41	16.48	26.50	15.50	24.91	14.25±2.66

[a] The individual subjects are represented as A–H. All subjects were Korean.
[b] Values represent the rates of decrease in blood glucose levels after 4 weeks from baseline (100%).

subjects have been reported, the antidiabetic effects of IGF-1, such as increasing insulin sensitivity and decreasing hemoglobin A1C, have been clearly demonstrated in many studies [11,20,21]. Plasma glucose reduction may have been ascribed to increased glucose clearance from plasma by peripheral tissues and decreased hepatic output of glucose. The effect of IGF-1 on plasma glucose reduction could be closely connected with increased adiponectin synthesis in adipocytes. Adiponectin may augment and mimic the metabolic actions of insulin by increasing fatty acid oxidation and insulin-mediated glucose disposal in skeletal muscle as well as by decreasing hepatic glucose output [22]. Moreover, among various ingredients in the BC, leptin was also able to reduce plasma glucose level. Shimomura et al.

Table 4
Effects of BC on total cholesterol, TGs and ketones in Type 2 diabetic patients

	Men			Women		
	Total cholesterol (mg/dl)	Triglycerides (mg/dl)	Ketone body (β-hydroxybutyric acid) (mmol/L)	Total cholesterol (mg/dl)	Triglycerides (mg/dl)	Ketone body (β-hydroxybutyric acid) (mmol/L)
Baseline	226.63±6.25	249.14±31.71	0.11±0.02	201.50±11.99	326.13±56.05	0.11±0.01
1 week	223.75±6.53	236.43±31.55	0.08±0.02	193.75±10.87	299.75±47.83	0.08±0.02
2 weeks	216.25±7.49	232.14±31.05	0.01±0.01	192.88±10.32	285.13±46.71	0.05±0.02
3 weeks	213.75±8.06	227.14±32.02	0.01±0.01	187±10.99	263.25±44.45	0.03±0.02
4 weeks	208.50±8.72	221.71±30.79	0.01±0.01	185.88±10.60	252.63±43.65	0.01±0.01
Decrease (%) [a]	8.27±1.43	11.96±2.58		7.62±0.75	21.46±3.53	

Data are means±S.E.M. (n=8).
[a] Values represent the rates of decrease in blood glucose levels after 4 weeks from baseline (100%).

[23] reported that exogenous leptin treatment not only reversed insulin resistance, but also increased concomitantly the insulin receptor substrate 2 (IRS-2) protein to a normal level. IRS-2 is essential for normal nutrient homeostasis because it mediates both peripheral insulin action and the effect of IGF-1 on β-cell growth. In addition, epidermal growth factor (EGF; 53-amino acid peptide) is present in human colostrum (200 mg/L), in milk (30–50 mg/L) and in the colostrum of many other species [24]. O'Loughlin et al. [25] reported that oral administration of EGF helped restore glucose transport and phlorizin binding in rabbit intestines after jejunal resection. Although most studies on the glucose-lowering effects of these growth factors and hormones were performed by intravenous administration, our results suggest that oral ingestion of BC could be biologically active in human. This opinion is in agreement with previous reports which suggested that colostrum supplementation would be a very beneficial treatment for diabetes, based on the fact that it can stimulate glucose utilization [26] and increase IGF-1 concentration [27]. Therefore, the action of these growth factors found in BC explains its effect of decreasing blood glucose levels in Type 2 diabetic patients, as shown in the present study. Table 3 shows that, with BC ingestion, the rate of decrease in blood glucose at 2 h postprandial was higher in the women than in the men, which may be due to a sexual dimorphism in glucose tolerance. In a recent study on gender differences in insulin-like growth factor axis response to a glucose load, women were less insulin sensitive and showed lower fasting free IGF-1 than men [28]. These results indicate that the management of blood glucose by IGF-1, which was administered with BC, could be more active in women than in men. However, further studies on sexual dimorphisms in blood glucose management are needed, according to interactions among insulin-like growth factor, insulin-like growth factor binding protein and liver enzymes.

Our data showed that the rate of decrease in blood glucose by BC was highest among the subjects with relatively high glucose levels within a test group. This suggests that the effect of BC on blood glucose is more pronounced in subjects with high blood glucose levels. However, this is open to discussion because this tendency was not shown in the 2 h postprandial blood glucose levels of the women.

In patients with diabetes and dyslipidemia, which are characterized by elevated TG levels, reduces insulin sensitivity and are associated with an increased risk of complications such as coronary heart disease and arteriosclerosis. Schernthaner [29] reported that normalization of cholesterol, as well as TGs, is essential for decreasing the elevated risk of coronary heart disease in people with metabolic syndromes or Type 2 diabetes. Therefore, diabetes treatment must be accompanied with the control of metabolic disorders that are related to increased levels of TGs and cholesterol, in addition to the normalization of blood glucose. As shown in the present study, BC can efficiently decrease TG and total cholesterol levels in Type 2 diabetic patients. A significant decrease in cholesterol concentration was also shown in a recent report on rats that received 10% BC, but there was no significant difference in TG concentration [30]. These results might be related to the interaction of various hormones within BC, such as leptin for fat breakdown. In fact, hepatic TG and cholesterol contents decreased linearly in mice that were administered leptin vs. saline treatments for 4 weeks [31].

Increase in TG mobilization, and the release of unesterified fatty acids from adipose tissue into the bloodstream are especially common in Type 2 diabetes [32]. Ketone bodies (acetoacetic acid, β-hydroxybutyric acid and acetone) are produced as byproducts when these fats are broken down for energy, and the risk of ketoacidosis is very high in Type 2 diabetic patients. Therefore, decrease in TGs may indicate increased oxidation of mobilized fatty acids with the formation of ketone bodies, or an inhibition of lipolysis [33]. However, our study showed that BC treatment significantly decreased β-hydroxybutyric acid as well as TGs and cholesterol. These results may be explained by decreases in enzyme activity related to ketone body formation, such as β-hydroxy-β-methylglutaryl-CoA synthase in the liver. However, this point remains to be further elucidated.

In conclusion, the present study demonstrated that BC has several properties for lowering the levels of TGs, total cholesterol and ketones, as well as blood glucose, in patients with Type 2 diabetes. It is notable that BC may have therapeutic potentials as an anti–Type 2 diabetes agent.

References

[1] Neel JV. Diabetes mellitus: a "thrifty" genotype rendered detrimental by "progress"? Am J Hum Genet 1962;14:353–62.

[2] Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002;346:393–403.

[3] Tuomilehto J, Lindstrom J, Eriksson JG, Valle TT, Hamalainen H, Ilanne-Parikka P, et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. N Engl J Med 2001;344:1343–50.

[4] Grundy SM, Benjamin IJ, Burke GL. Diabetes and cardiovascular disease: a statement for healthcare professionals from the American Heart Association. Circulation 1999;100:1134–46.

[5] Kendall DM, Bergenstal RM. Comprehensive management of patients with type 2 diabetes: establishing priorities of care. Am J Manag Care 2001;7(10 Suppl):S327–43.

[6] Siegel RD, Cupples A, Schaefer EJ. Lipoproteins, apolipoproteins, and low-density lipoprotein size among diabetics in the Framingham Offspring Study. Metabolism 1996;45:1267–72.

[7] Rosenson RS, Shott S, Lu L. Hypertriglyceridemia and other factors associated with plasma viscosity. Am J Med 2001;110:488–92.

[8] Ronge H, Blum JW. Somatomedin C and other hormones in dairy cows around parturition, in newborn calves and in milk. J Anim Physiol Nutr 1988;60:168.

[9] Campbell PG, Baumrucker CR. Insulin-like growth factor-I and its association with binding proteins in bovine milk. J Endocrinol 1989; 120:21–9.

[10] Collier RJ, Ganguli S, Menke PT, Buonomo FC, McGrath MF, Kotts CE, et al. Changes in insulin and somatomedin receptors and uptake of

insulin, IGF-1 and IGF-11 during mammary growth, lactogenesis and lactation. In: Heap RB, Prosser CG, Lamming GE, editors. Biotechnology in growth regulation. London, England: Butterworths; 1989. p. 153–63.

[11] Frystyk J. Free insulin-like growth factors — measurements and relationships to growth hormone secretion and glucose homeostasis. Growth Horm IGF Res 2004;14:337–75.

[12] Janssen JA, Lamberts SW. The role of IGF-I in the development of cardiovascular disease in type 2 diabetes mellitus: Is prevention possible? Eur J Endocrinol 2002;146:467–77.

[13] Tan K, Baxter RC. Serum insulin-like growth factor I levels in adult diabetic patients: the effect of age. J Clin Endocrinol Metab 1986;63: 651–5.

[14] Dagago-Jack S, Liu J, Askaria H, Tykodi G, Umamaheswaran I. Impaired leptin response to glucocorticoid as a chronic complication of diabetes. J Diab Complic 2000;14:327–32.

[15] Fox C, Esparza J, Nicolson M, Bennett PH, Schulz LO, Vanencia ME, et al. Plasma leptin concentrations in Pima Indians living in drastically different environments. Diabetes Care 1999;22:413–7.

[16] Ragab SS. Anti-diabetic influence of bovine colostrum in streptozotocin induced diabetic rats. Egypt J Nutr 2002;17:229–54.

[17] SAS Institute. SAS/STAT User's Guide. Version 6.12. Cary (NC): SAS Inst. Inc; 1996.

[18] Neil A, Hawkins M, Potok M, Thorogood M, Cohen D, Mann J. A prospective population-based study of microalbuminuria as a predictor of mortality in NIDDM. Diabetes Care 1993;16:996–1003.

[19] Salminen E, Karonen SL, Salminen S. Blood glucose and plasma insulin responses to fat free milk and low-lactose fat free milk in healthy human volunteers. Zeitschrift für Ernährungswissenschaft 1987;26:52–5.

[20] rhIGF-I in NIDDM Study (RINDS) Group. Evidence from a dose-ranging study that recombinant insulin-like growth factor I (rhIGF-I) effectively and safely improves glycemic control in non-insulin dependent diabetes mellitus. Diabetes 1996;45(Suppl 1):27A [Abstract].

[21] Woods KA, Camacho-Hubner C, Bergman RN, Barter D, Clark AJ, Savage MO. Effects of insulin-like growth factor I (IGF-I) therapy on body composition and insulin resistance in IGF-I gene deletion. J Clin Endocrinol Metab 2000;85:1407–11.

[22] Chen H, Montagnani M, Funahashi T. Adiponectin stimulates production of nitric oxide in vascular endothelial cells. J Biol Chem 2003;278:45021–6.

[23] Shimomura I, Matsuda M, Hammer RE, Bashmakov Y, Brown MS, Goldstein JL. Down regulation of IRS-2 and up-regulation of SREBP-1c leads to mixed insulin resistance and sensitivity in livers of lipodystrophic and ob/ob mice. Mol Cell 2000;6:77–86.

[24] Playford RJ, Macdonald CE, Johnson WS. Colostrum and milk-derived peptide growth factors for the treatment of gastrointestinal disorders. Am J Clin Nutr 2000;72:5–14.

[25] O'Loughlin W, Winter M, Shun A. Structural and functional adaptation following jejunal resection in rabbits: effect of epidermal growth factor. Gastroenterology 1994;107:87–93.

[26] Dohm GL, Elton CW, Raju MS, Mooney ND, DiMarchi R, Pories WJ, et al. IGF-1 stimulated glucose transport in human skeletal muscle and IGF-I resistance in obesity and NIDDM. Diabetes 1990; 39:1028–32.

[27] Mero A, Miikkulainen H, Riski J, Pakkanen R, Aalto J, Takala T. Effects of bovine colostrum supplementation on serum IGF-1, IgG, hormone, and saliva IgA during training. J Appl Physiol 1997;83: 1144–51.

[28] Flanagan DE, Holt RIG, Owens PC, Cockington RJ, Moore VM, Robinson JS, et al. Gender differences in the insulin-like growth factor axis response to a glucose load. Acta Physiol 2006;187:371–8.

[29] Schernthaner G. Is dyslipidaemia important if we control glycaemia? Atherosclerosis 2005(Suppl 6):3–10.

[30] Davis PF, Greenhill NS, Rowan AM, Schollum LM. The safety of New Zealand bovine colostrum: nutritional and physiological evaluation in rats. Food Chem Toxicol 2007;45:229–36.

[31] Hyogo H, Roy S, Paigen B, Cohen DE. Leptin promotes biliary cholesterol elimination during weight loss in *ob*/*ob* mice by regulating the enterohepatic circulation of bile salts. J Biol Chem 2002;277: 34117–24.

[32] Mellado V, Lozoya M. Effect of the aqueous extract of *Cecropia obtusifolia* on blood sugar of normal and pancreatectomized dogs. Int J Crude Drug Res 1984;22:11–6.

[33] Al-Awadi FM, Shoukry M. The lipid lowering effect of an anti-diabetic plant extract. Diabetologia 1988;25:1–5.