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INFLUENCE OF CAMEL MILK ON GLYCOPROTEIN COMPONENTS IN STREPTOZOTOCIN-DIABETIC RATS

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ABSTRACT

Camel milk is different from other ruminant milk; having low cholesterol; low sugar; high minerals especially zinc; high vitamin C; low protein and large concentrations of insulin. In Saudi Arabia, camel milk is traditionally used for many medical approaches. In the long-term effect of camel milk in type 2 diabetic rats on antihyperglycaemic, antioxidants, antihyperlipidaemic, and membrane bound ATPases was investigated, and its effect was shown in our previous study. The levels of glycoproteins were altered in experimental diabetes mellitus. Diabetes was induced in albino Wistar rats by a single intraperitoneal injection of streptozotocin (STZ) (40 mg/kg body weight). Diabetic rats exhibited significantly ($P<0.05$) increased levels of plasma glucose and decreased levels of plasma insulin. Also, significantly ($P<0.05$) increased levels of glycoproteins (hexose, hexosamine, fucose and sialic acid) were observed in serum, liver, and kidney of diabetic rats. Rats were treated with camel milk (250 ml/day) for a period of 45 days. Diabetic rats treated with camel milk showed significantly ($P<0.05$) decreased levels of glucose and glycoproteins and increased levels of insulin after 45 days. A similar effect was observed in diabetic rats treated with glibenclamide (600 µg/kg body weight). Normal rats treated with camel milk (250 ml/day) did not show any significant ($P<0.05$) effect on glucose, insulin and glycoproteins. The results of our study showed that camel milk has the potential to reduce glucose and glycoproteins levels and increase insulin levels in STZ-induced experimental diabetes mellitus in rats.

Key words: Camel milk, diabetes mellitus, glycoproteins, insulin, streptozotocin, wistar rats

Diabetes mellitus is one of the most common chronic diseases in both western and developing countries. This metabolic disorder is characterised by hyperglycaemia and disturbances of carbohydrate, protein and fat metabolism, secondary to an absolute or relative lack of insulin (Alberti and Zimmet, 1998). Diabetes is a serious global problem which kills more than 3.8 million people annually (International Diabetes Federation, 2006). The situation is set to worsen with the total number of diabetes-related deaths estimated to increase by more than 50 percent over the next decade (World Health Organisation, 2008). The majority of the new cases will be those with type 2 diabetes and most of these will be in China, the Indian subcontinent and Africa. It is estimated that from 65 million cases of type 2 diabetes in Asia and Oceania in 1995, the number will double to 135 million by 2010 (Zimmet, 2003). Saudi Arabia, a country undergoing a rapid epidemiologic transition, is witnessing a steady increase in the prevalence of diabetes mellitus with the recent estimate of prevalence being as high as 23.7% among adult citizens (Al-Nozha *et al,* 2004).

Streptozotocin (STZ) is often used to induce diabetes mellitus in experimental animals through its toxic effects on pancreatic β-cells. STZ-induced diabetes mellitus is associated with the generation of reactive oxygen species causing oxidative damage (Szkudelski, 2001). Diabetics and experimental animal models exhibit high oxidative stress due to persistent and chronic hyperglycaemia, which thereby depletes the activity of antioxidative defense system and thus promotes de novo free radicals generation (Baynes and Thorpe, 1997). Under diabetic conditions, reactive oxygen species are produced mainly through glycation reaction which occurs in various tissues and may play an important role in the development of diabetic complications (Baynes, 1991). Advanced glycation end products (AGEs) modify galactose, fucose and sialic acid contents of specific cellular glycoproteins (Rellier *et al,* 1999).

Treatment of diabetes mellitus presently relies upon compounds from a number of chemical classes such as sulfonylureas, non-sulfonylureas, biguanides, etc. Many of the oral agents that are presently in use for the treatment of diabetes mellitus suffer from

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implication in a number of serious and adverse effects (Zhang and Moller, 2000). The primary treatment for diabetes mellitus is insulin replacement, however at present neither entire physiological insulin replacement could be achieved in clinical practice nor could metabolic disturbances be normalised. Hence, some diabetic patients adopt alternative treatments in the context of traditional ethno-medical practices (Agrawal *et al,* 2003).

Camel milk may be a therapeutic adjunctive option for diabetes mellitus in humans (Agrawal *et al,* 2005). Agrawal *et al* (2003) had reported that camel milk supplementation to type 1 diabetic patients proved effective in reducing glucose levels. Reduction in the occurrence of diabetes mellitus in a population consuming camel milk was reported (Breitling *et al,* 2002). A study by Agrawal *et al* (2004) had shown the hypoglycemic activity of camel milk in STZ-induced diabetic rats. The hypoglycaemic activity of camel milk in chemically pancreatectomised rats was also reported by Agrawal *et al,* (2005). In our early study, camel milk exhibited antihyperglycaemic (Khalid *et al,* 2011) and antioxidant properties (Khalid *et al,* 2010)], hypolipidaemic action (Khalid *et al,* 2010), membrane bound ATPases (Khalid *et al,* 2010) and collagen abnormalities (Khalid *et al,* 2011) in streptozotocin-diabetic rats after 45 days of treatment.

The present study evaluated the effect of camel milk on plasma glucose and insulin and on glycoproteins (hexose, hexosamine, fucose and sialic acid) in serum and tissues (liver and kidney) of STZ-induced diabetic albino Wistar rats.

Materials and Methods

Male albino rats of Wistar strain of body weight ranging from 180 to 200 g were procured from Central Animal House, King Saud University and they were maintained in an air conditioned room (25 ± 1°C) with a 12 h light/12 h dark cycle. Feed and water were provided *ad libitum*. Procedures involving animals and their care were accordance with the Policy of Research Centre, King Saud University. Streptozotocin was purchased from Sigma-Aldrich, St. Louis, USA. All other chemicals were of analytical grade.

The animals were rendered diabetic by a single intraperitoneal injection of streptozotocin (40 mg/kg bodyweight) in freshly prepared citrate buffer (0.1 M, pH 4.5) after an overnight fast. STZ injected animals were given 20% glucose solution for 24 h to prevent initial drug-induced hypoglycaemic mortality. STZ injected animals exhibited massive glycosuria (determined by Benedict's qualitative test) and diabetes in STZ rats was confirmed by measuring the fasting plasma glucose concentration, 96 h after injection with STZ. The animals with plasma glucose above 240 mg/dl were considered diabetic and used for the experiment.

The animals were randomly divided into five groups of six animals each as given below. Rats of groups II and IV were fed with 250 ml of raw camel milk daily for 45 days through watering bottle instead of water. Whereas animals in groups I, III and V were given tap water for 45 days, and rats of group V were given 600 µg/kg body weight of glibenclamide by orally once in a day in the morning for 45 days.

Group I: Normal control (water)

Group II: Normal + raw camel milk (250 ml/day)

Group III: Diabetic control

Group IV: Diabetic rats + raw camel milk (250 ml/day)

Group V: Diabetic rats + glibenclamide (600 µg/kg body weight/day)

After 45 days of treatment, the animals were fasted for 12 h, anaesthetised between 8 a.m. to 9 a.m. using ketamine (24 mg/kg body weight, intramuscular injection), and sacrificed by decapitation. Blood was collected in a dry test tube and allowed to coagulate at ambient temperature for 30 min. Blood was also collected in tubes with a mixture of potassium oxalate and sodium fluoride (1:3) for the estimation of plasma insulin and glucose. Liver and kidney were excised immediately from the rats and stored at -20°C until use.

Plasma glucose was estimated by the method of Trinder using a reagent kit (Trinder, 1969). Plasma insulin was measured by the method of Burgi *et al* (1988).

The tissue samples were defatted prior to estimation. A weighed amount of defatted tissue was suspended in 3.0 ml of 2 N HCl and heated at 90°C for 4 h. The sample was cooled and neutralized with 3.0 ml of 2 N NaOH. Aliquots from this were used for estimation of hexose, hexosamine and sialic acid. Protein-bound hexoses were estimated by the method of Dubois and Gilles (1956). Protein bound hexosamine was estimated by the method of Wagner (1979). Sialic acid in was estimated by the method of Warren (1959). Fucose was estimated by the method of Dische and Shettle (1948).

Values were given as means ± SD for six rats in each group. Data were analysed by one-way analysis of variance followed by Duncan's Multiple Range Test (DMRT) using SPSS version 11 (SPSS, Chicago, IL). The limit of statistical significance was set at $P < 0.05$.

Results and Discussion

Table 1 shows the effect of administration of camel milk for 45 days on plasma glucose and insulin in normal and streptozotocin-diabetic rats. Plasma glucose significantly increased and insulin levels were decreased in diabetic rats. Both camel milk and glibenclamide significantly brought down the plasma glucose toward normal level and increased insulin levels in streptozotocin-diabetic rats. Natural food with antihyperglycaemic activities has been increasingly used by diabetic patients and health care professionals worldwide as an alternative approach (Lee *et al,* 2004; Ribnicky *et al,* 2005). Studies emerged from laboratory showed that administration of camel milk to diabetic rats reduced glucose levels and increased insulin levels. The hypoglycemic activity of camel milk may be because of high concentrations of insulin like protein as it contains about 45-128 units/liter (Singh, 2001). It also contains high amount of zinc (Mehaia *et al,* 1995). Zinc plays a major role of insulin secretory activity in pancreatic beta cells. Previous report shows that zinc supplementation attenuates insulin secretory activity in pancreatic islets of the ob/ob mouse (Begin-Heick *et al,* 1985) and also Richards-Williams *et al* (2008) reported that, extracellular ATP and zinc are co-secreted with insulin and activate multiple P2X purinergic receptor channels expressed by islet beta-cells to potentiate insulin secretion. Chen *et al* (1998) reported that, zinc supplementation alleviated hyperglycemia of ob/ob mice, which may be related to its effect on the enhancement of insulin activity.

Present study shows that increased insulin levels may be due to the insulin like protein and high amount of zinc present in camel milk. Our findings are in agreement with Agrawal *et al* (2004), who reported that camel milk administration to diabetic rats increased body weight and decreased plasma glucose level in STZ diabetic rats after receiving 250 ml of camel milk daily for 22 days. Oral insulin has been known since many years but the critical draw back is its coagulum formation in acidic media in stomach, which neutralises its potency. One property of camel milk is that it does not form the coagulum in the stomach or the acidic media; thereby it prevents degradation of insulin in the stomach. Beg *et al* (1989), who studied that amino acid sequence of some of the camel milk protein, reported that it is rich in half cystine, which has superficial similarity with insulin family of peptides.

Tables 2 and 3 represent the levels of sialic acid and hexosamines in the plasma and tissues (liver and kidney) of normal and diabetic rats. The diabetic rats had increased levels of sialic acid and hexosamines in the plasma and tissues except kidney, in which

Table 1. Effect of camel milk on plasma glucose and insulin levels in normal and STZ-diabetic rats.

Groups	Glucose (mg/dl)		Insulin (µU/ml)
	Day 0	Day 45	
Normal	69.65 ± 02.07	76.32 ± 07.59^{a}	15.39 ± 1.31^{a}
Normal +camel milk (250 ml/day)	68.02 ± 04.94	75.45 ± 07.76^{a}	15.29 ± 1.30^{a}
Diabetic control	251.25 ± 15.80	292.38 ± 19.20^{b}	5.53 ± 0.41^{b}
Diabetic+camel milk (250 ml/day)	248.95 ± 17.92	141.57 ± 12.82^{c}	9.97 ± 0.80^{c}
Diabetic + glibenclamide (600 µg/kg b.wt)	255.09 ± 14.60	106.22 ± 8.68^{d}	14.88 ± 1.26^{a}

Values are means ± S.D for six rats.
Values not sharing a common superscript differ significantly at $P < 0.05$ (DMRT).

Table 2. Effect of camel milk on sialic acid in serum and tissues of normal and STZ-diabetic rats.

Groups	Serum (mg/dl)	Liver (mg/100 g)	Kidney (mg/100 g)
Normal	45.44 ± 3.06^{a}	10.08 ± 0.31^{a}	8.03 ± 0.52^{a}
Normal + camel milk (250 ml/day)	44.25 ± 2.38^{a}	10.56 ± 0.68^{a}	8.21 ± 0.56^{a}
Diabetic control	69.24 ± 2.45^{b}	21.12 ± 1.15^{b}	4.64 ± 0.35^{b}
Diabetic + camel milk (250 ml/day)	58.06 ± 2.69^{c}	16.04 ± 0.75^{c}	6.15± 0.42^{c}
Diabetic + glibenclamide (600 µg/kg b.wt)	51.15 ± 2.03^{d}	13.9 ± 0.73^{d}	7.75 ± 0.50^{a}

Values are means ± S.D for six rats.
Values not sharing a common superscript differ significantly at $P < 0.05$ (DMRT).

Table 3. Effect of camel milk on hexosamine in serum and tissues of normal and STZ-diabetic rats.

Groups	Serum (mg/dl)	Liver (mg/100 g)	Kidney (mg/100 g)
Normal	49.33 ± 2.10[a]	8.62 ± 0.51[a]	5.58 ± 0.42[a]
Normal + camel milk (250 ml/day)	48.44 ± 2.93[a]	8.47 ± 0.65[a]	5.51 ± 0.33[a]
Diabetic control	65.33 ± 2.52[b]	17.51 ± 1.17[b]	13.21 ± 1.0[b]
Diabetic + camel milk (250 ml/day)	57.33 ± 3.24[c]	10.84 ± 0.90[c]	7.81 ± 0.49[c]
Diabetic + glibenclamide (600 µg/kg b.wt)	48.66 ± 1.68[a]	8.03 ± 0.30[a]	6.40 ± 0.53[a]

Values are means ± S.D for six rats.
Values not sharing a common superscript differ significantly at $P < 0.05$ (DMRT).

Table 4. Effect of camel milk on fucose in serum and tissues of normal and STZ-diabetic rats.

Groups	Serum (mg/dl)	Liver (mg/100 g)	Kidney (mg/100 g)
Normal	12.04 ± 0.93[a]	14.81 ± 0.84[a]	11.76 ± 0.61[a]
Normal + camel milk (250 ml/day)	11.72 ± 0.84[a]	12.38 ± 0.50[a]	12.03 ± 0.97[a]
Diabetic control	19.64 ± 0.84[b]	27.73 ± 0.96[b]	30.76 ± 1.01[b]
Diabetic + camel milk (250 ml/day)	15.06 ± 1.23[c]	20.23 ± 0.88[c]	20.16 ± 0.83[c]
Diabetic + glibenclamide (600 µg/kg b.wt)	13.18 ± 0.59[ac]	15.28 ± 0.95[a]	17.87 ± 1.01[d]

Values are means ± S.D for six rats.
Values not sharing a common superscript differ significantly at $P < 0.05$ (DMRT).

Table 5. Effect of camel milk on hexose in serum and tissues of normal and STZ-diabetic rats.

Groups	Serum (mg/dl)	Liver (mg/100 g)	Kidney (mg/100 g)
Normal	110.08 ± 9.46[a]	22.08 ± 1.77[a]	21.57 ± 1.60[a]
Normal + camel milk (250 ml/day)	102.51 ± 10.04[ac]	21.70 ± 1.56[a]	21.04 ± 1.42[a]
Diabetic control	163.87 ± 14.49 [b]	36.60 ± 1.72[b]	39.00 ± 2.20[b]
Diabetic + camel milk (250 ml/day)	142.66 ± 9.61[d]	28.90 ± 1.60[c]	29.91 ± 1.01[c]
Diabetic + glibenclamide (600 µg/kg b.wt)	119.93 ± 8.86[ae]	24.48 ± 2.14[d]	23.61 ± 1.59[d]

Values are means ± S.D for six rats.
Values not sharing a common superscript differ significantly at $P < 0.05$ (DMRT).

sialic acid decreased, and the treatment with camel milk and glibenclamide showed reversal of these parameters toward normal.

Tables 4 and 5 represent the levels of fucose and total hexoses in the plasma and tissues (liver and kidney) of normal and diabetic rats. The diabetic rats had increased levels of fucose and total hexoses in the plasma and tissues, and the treatment with camel milk and glibenclamide showed reversal of these parameters toward normal. Glycoproteins are carbohydrate linked protein macromolecules found in the cell surface, which is the principal component of animal cells. They play an important role in membrane transport, cell differentiation and recognition, the adhesion of macromolecules to the cell surface, and the secretion and absorption of macromolecules (Mittal *et al,* 1996). The oligosaccharide moieties of glycoproteins: hexose, hexosamine, fucose and sialic acid have an important role in protein stability, function, and turnover (Wiese *et al,* 1997). The level of different types of serum glycoproteins are maintained within a narrow range in health (Sharma and Sur, 1967), but are elevated in diabetes mellitus (Anand *et al,* 1985). Abnormal levels of glycoproteins are important in the pathogenesis of liver and kidney diseases in diabetes (Pari and Saravanan, 2006).

In this study, elevated levels of glycoproteins are observed in serum, liver and kidney in diabetic rats. Increased glycosylation of various proteins in diabetic patients had been reported earlier (Rahman *et al,* 1990). The increase in serum glycoprotein components have been associated with the severity and duration of diabetes. In hyperglycaemia, free amino groups of proteins react slowly with the carbonyl groups of reducing sugars such as glucose, to yield a Schiff-base intermediate (Maillard reaction). These Schiff-base intermediates undergo Amadori rearrangement to stable ketoamine derivative (fructosamine) (Bucala, 1999). Rahman *et al* (1990) have shown increased serum fructosamine concentrations in diabetic patients.

Fucose is a member of the group of eight essential sugars the body requires for optimal function of cell-to-cell communication and its metabolism appears to be altered in various diseases such as diabetes mellitus (Mondoa *et al,* 2001). A raise in fucose levels could be due to increased glycosylation in the diabetic state (Hunt *et al,* 1991). Elevated levels of fucose in experimental diabetes were reported by other researchers (Prakasam *et al,* 2005). Sialic acid is found in a wide variety of substances and tissues in animals and humans, occurring most abundantly in glycoproteins and glycolipids. Sialic acid bound to membrane glycoproteins and glycolipids apparently enters the circulation by either shedding or cell lysis (Sheshadri, 1994). Increased levels of sialic acid were reported in STZ-induced diabetic rats (Gorgun *et al,* 2002) and in diabetic patients (Ekin, 2003).

In the diabetic state, deficiency of insulin secretion causes derangement of glycoprotein metabolism that result in the basal membrane thickening. Excess availability of glucose in the hyperglycemic state accelerates the synthesis of basement membrane components, i.e. glycoproteins (Spiro and Spiro, 1971). Camel milk treatment to diabetic rats decreased the levels of glycoproteins in serum and tissues. Decreased hyperglycaemic state with increased levels of plasma insulin observed in camel milk-treated diabetic rats might be responsible for the decrease of glycoproteins in serum, liver and kidney. In this context, other researchers have shown that decrease in hyperglycemia could lead to a decrease in glycoprotein levels (Prakasam *et al,* 2005). For all the parameters studied, diabetic rats treated with glibenclamide (600 µg/kg body weight) exhibited a similar effect to camel milk (250 ml/day).

Conclusion

The results of study show that camel milk possesses glucose lowering effect in STZ-induced diabetes mellitus in rats. It also increased plasma insulin levels and decreased glycoproteins in serum, liver and kidney. This could be due to the presence of insulin like protein in camel milk and also due to the high concentration of zinc.

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