

## Effect of camel milk on blood glucose, cholesterol and total proteins variations in alloxan-induced diabetic dogs

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### Abstract

The efficacy of camel milk on alloxan-induced diabetic dogs was evaluated in this study. Firstly, two diabetic groups of dogs received raw camel milk (group 1) or raw cow milk (group 2). One healthy group was used as control in which dogs received raw camel milk. Five hundred ml of raw milk were given to the animals daily for five weeks. By the end of the first test, group 1 showed a statistically significant decline in blood glucose (from  $10.88 \pm 0.55$  mmol/l to  $5.77 \pm 0.44$  mmol/l); cholesterol (from  $5.99 \pm 0.15$  mmol/l to  $4.4 \pm 0.62$  mmol/l) and in total proteins concentrations (from  $80.06 \pm 2.11$  g/l to  $63.56 \pm 3.16$  g/l). In this period, group 2 showed high blood glucose (8 mmol/l), cholesterol (from  $5.99 \pm 0.58$  to  $7.13 \pm 1.25$  mmol/l) and total proteins concentrations (from  $79.18 \pm 6.07$  to  $84.33 \pm 0.56$  g/l). This diabetic state was confirmed by Intraperitoneal glucose tolerance test. These dogs (group 2) were treated, in test 2, with camel milk instead of bovine milk and showed an improvement in blood glucose (from  $9.83 \pm 0.72$  mmol/l before drinking milk to  $7.83 \pm 0.88$  mmol/l in week 4), proteins and lipids profiles. Dogs from group 1, which were used to follow the effect of camel milk by the end of experiment, showed healthy state: normal blood glucose levels (5.16–6.5 mmol/l), cholesterol (4.14–5.51 mmol/l), triglycerides (0.51–1.21 mmol/l) and total proteins concentrations (60.77–69.18 g/l). It is obvious in this study that camel milk has a therapeutic effect on alloxan-induced diabetic dogs.

**Key words:** Camel milk, cow milk, alloxan, diabetes, dog.

### Introduction

Diabetes mellitus is a chronic disorder of metabolism caused by an absolute or relative lack of insulin. It is characterized by hyperglycemia in the postprandial and or fasting state and in its severe form is accompanied by ketosis and protein wasting.<sup>1</sup> This metabolic disorder can be induced chemically using alloxan or streptozotocin. Alloxan diabetes is caused by the selective pancreatic beta cell toxicity of this composite.<sup>2,3</sup> In order to destroy insulin-producing cells and to induce a state of insulin-dependent diabetes mellitus, alloxan due to its similarity in molecular shape with the glucose molecule, must be taken up into the cell via the low affinity GLUT 2 glucose transporters in the plasma membrane.<sup>4</sup>

Several species such as rats, rabbit and dogs are sensitive to alloxan toxicity.<sup>5</sup>

Besides drugs classically used for the treatment of diabetes (insulin, sulphonylureas and biguanides) camel milk is known, in arid regions and in the wilderness, for its usefulness to treat diabetes mellitus. For example, an Indian

study reported a hypoglycemic effect of camel milk on diabetic rats.<sup>6,7</sup>

In this context, this study was conducted to test the effect of camel milk in comparison to cow milk in alloxan - induced diabetic dogs.

Alloxan-diabetic dog was used because, as mentioned in literature, it is a model of insulin deficiency and insulin resistance while simulating postprandial conditions in diabetic patients.<sup>8,9</sup>

### Material and Methods

**Animals and diet:** Clinically normal adult mixed-breed dogs were prepared for this experiment. Their body weight ranged from 12 to 16 kg initially.

These dogs were housed individually in the Tunisian Veterinary Medicine School, Sidi Thabet. Animals were fed once daily with 350–400 g of commercial dry food (23% protein, 6% fat, 33% carbohydrates, 4% crude fiber and 3000 kcal/kg as energetic value; (DOGSY) from Tunisian Animal Nutrition Society) and 400 g of beef.

This food was given to all dogs daily in the morning after drinking milk. The quantity of milk given to the dogs was the same. Water was available for dogs throughout the duration of the experiment *ad libitum*.

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### Experimental design

This experimental study was divided into two tests, the first test lasted five weeks and the second test lasted seven weeks.

### Milk samples

Camel milk used during this study was obtained from a camel herd (*Camelus dromedarius*) belonging to the Arid Land Institute (Medenine, Tunisia) and cow milk was given from a Tunisian breed of cow housed in the Veterinary School of Medicine, Sidi Thabet, Tunisia. The two types of milk were used fresh without any treatment or dilution.

Before distribution of raw milk to the animal, the pH and acidity of the milk sample was checked to monitor the freshness of milk. The gross composition of the two types of milk was determined (fat, total proteins and total solids). Fat content was measured using the Neusol method.<sup>10</sup> and the total proteins concentration was determined by the Kjeldahl method using a nitrogen conversion factor of 6.36.<sup>11</sup> Total solids were evaluated after drying at 105°C until a steady weight was achieved.<sup>11</sup>

### Induction of diabetes

After overnight fasting, the dogs were injected by an intravenous administration of 65 mg/kg of body weight of alloxan monohydrate (Sigma, Aldrich; Germany).<sup>2, 4</sup> The alloxan solution was prepared by dissolving it in normal saline at a concentration of 100 mg/ml and injected freshly after filtration. Seven days later, these animals showed a diabetic state characterized by a high fasting blood glucose (>10 mmol/l) and a notable glucose level in urine (+++).

### Test 1: Essay of Hypoglycemic activity of camel milk

Twelve adult dogs (mean body weight 14 kg; range 12 to 16 kg) were divided into 3 groups: group 1 consisted of 4 diabetic dogs drinking camel milk. Group 2 consists of 4 diabetic dogs receiving cow milk and group 3 contained 4 healthy dogs drinking camel milk and used as control. Each animal received 500 ml of milk daily, every morning for five weeks.

#### • Injection of Can-insulin

Can-insulin® (by Intervet) was injected to the dogs from group 2 (treated with cow milk) as indicated in the notice: subcutaneously with (1 IE/kg of body weight + 3 IE) at feeding. Can-Insulin was injected to maintain blood glucose level to less than 10 mmol/l.

#### • Intravenous Glucose Tolerance Test: IGTT

An Intravenous Glucose Tolerance Test (IGTT) assay was performed aiming to verify the glycemic state (diabetic or not) of the animals. This test was performed, by the end of the first test and before the beginning of the second, to confirm the glycemic status of all animals.

Glucose was injected after an overnight fasting, by intravenous administration of 0.5g of glucose/kg of body weight. Blood sample was drawn each 30 min for 3 hours.<sup>12</sup>

### Test 2: Effect of camel milk on diabetic dogs treated previously with cow milk

By the end of the second trial, each dog from group 2 was given 500 ml of camel milk daily for five weeks (group 2 + camel milk).

In this test we also used dogs from group 1 from the previous test (test 1) in order to control the variations of blood glucose, cholesterol, TG and total proteins levels for a longer period after stopping camel milk.

This test was divided into two components: period 1 during the first five weeks in which animals from group 2 were treated with camel milk and period 2 lasting 3 weeks after cessation of the milk.

### Blood samples

Blood samples were drawn 2 times per week from the radial vein with the vacutainer system. The samples were divided into two tubes: one for glycemic assay (enclose oxalate fluoride), the other for cholesterol, triglycerides (TG) and total protein assays.

### Serum analysis

The blood glucose concentration was measured by a glucose oxidase method (Biomaghreb®) using a spectrophotometer at 505 nm.

Cholesterol and triglycerides concentrations were determined by enzymatic methods (Biomaghreb®) using CECIL spectrophotometer (CE 2041, Cecil Instruments, England) at 505 nm. Total protein concentrations were analyzed at 546 nm.

### Urine analysis

During the first week after injection of alloxan, urine samples were subjected to analyze glucose, proteins and ketones. These analyses were performed using Bayer Strips for urine analysis.

### Statistical analysis

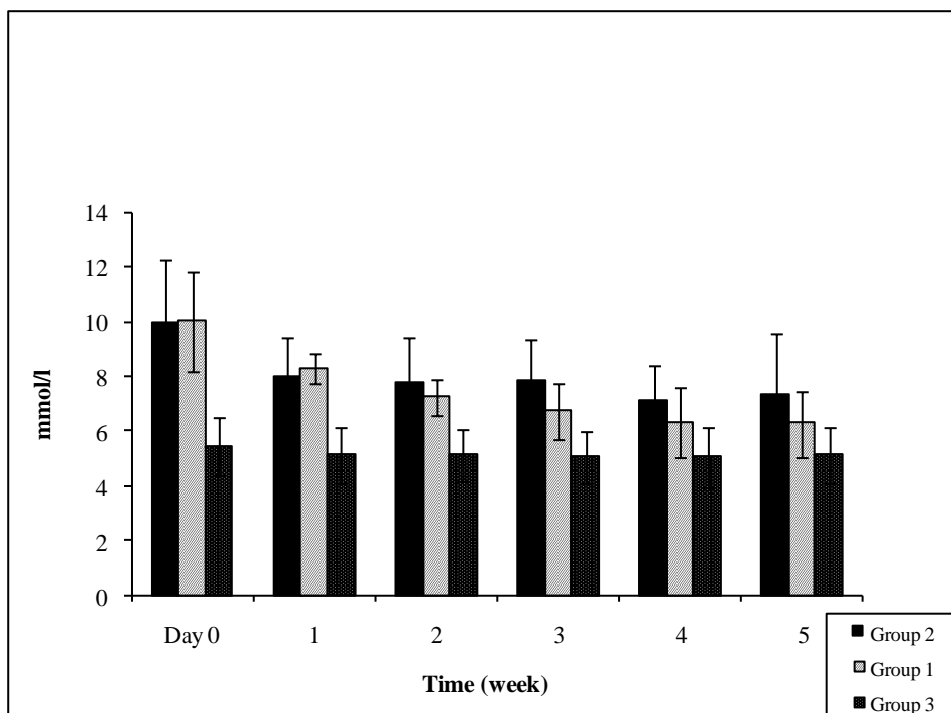
The data were expressed as the mean ± SEM and represent the average values for the animals in the same group. Each analysis was repeated three times and the average was used to compare between treatment groups. These data were subjected to statistical analysis using SAS computer software (SAS institute, 1998) and the data were compared between and within the experimental groups.

This test combines ANOVA with comparison of differences between the means of the treatments at the significance level of  $p < 0.05$ .

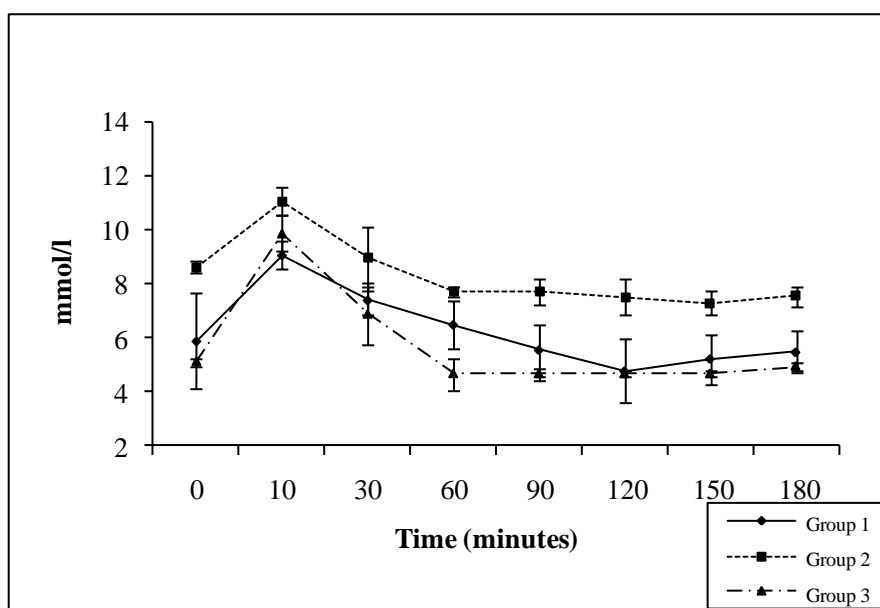
## Results

### Gross chemical composition of milk

The pH and acidity of the camel milk provided to the animals were  $6.41 \pm 0.18$  and  $16.87 \pm 1.035^\circ$  Dornic, respectively. These parameters for the cow milk were as follows:  $6.61 \pm 0.24$  for pH and  $17.12 \pm 0.64^\circ$  Dornic for acidity



**Fig 1:** Weekly variations of blood glucose levels in groups 1, 2, and 3 during the first trial. Group 1: Diabetic dogs treated with camel milk. Group 2: Diabetic dogs receiving cow milk and treated with Can-insulin. Group 3: Healthy dogs receiving camel milk.



**Fig 2:** IGTT test in group 1, 2, and 3 by the end of first trial. Group 1: Diabetic dogs treated with camel milk. Group 2: Diabetic dogs receiving cow milk and treated with Can-insulin. Group 3: Healthy dogs receiving camel milk.

The camel milk used during this study was rich in total protein ( $34.15 \pm 3.11$  g/l), and total solids ( $119.43 \pm 1.84$  g/l) compared with bovine milk ( $30.5 \pm 1.95$  g/l for total proteins and  $104.88 \pm 4.39$  g/l for total solid amounts). There was no significant difference in fat between the camels.

**Test 1: Effect of camel milk compared with cow milk on alloxan induced-diabetic dogs**

After one week of the injection of alloxan, a stable diabetes

was shown on all dogs illustrated by high blood glucose level ( $\geq 10.0$  mmol/l), glucosuria (+++), proteinuria (+++) and ketones in urine (++)

After drinking camel milk for five weeks, group 1 showed statistically significant decrease in blood glucose levels (from  $10.88 \pm 0.5$  mmol/l to  $5.77 \pm 0.44$  mmol/l;  $p < 0.05$ ; figure 1); in total cholesterol (from  $6.17 \pm 0.15$  mmol/l to  $4.35 \pm 0.61$  mmol/l;  $p < 0.05$ ) and in total proteins (from  $80.16 \pm 2.11$  g/l to  $63.93 \pm 2.61$  g/l), (table 1).

**Table 1:** Weekly variations of total protein, cholesterol and triglycerides (TG) concentrations during the first test

	Total proteins (g/l)			Cholesterol (mmol/l)			TG (mmol/l)		
	Group 1	Group 2	Group 3	Group 1	Group 2	Group 3	Group 1	Group 2	Group 3
Day 0	80.16 <sup>a</sup> ±2.11	79.18 <sup>a</sup> ±6.07	68.48 <sup>b</sup> ±2.11	6.17 <sup>a</sup> ±0.5	5.99 <sup>a</sup> ±0.58	4.17 <sup>b</sup> ±1.2	1.03 <sup>a</sup> ±0.27	1.03 <sup>a</sup> ±0.17	0.95 <sup>a</sup> ±0.27
Week 1	74.35 <sup>a</sup> ±7.25	81.5 <sup>a</sup> ±3.81	68.8 <sup>b</sup> ±3.25	5.9 <sup>a</sup> ±0.15	6.09 <sup>a</sup> ±1	3.98 <sup>b</sup> ±0.25	0.82 <sup>a</sup> ±0.22	1.29 <sup>a</sup> ±0.19	0.64 <sup>a</sup> ±0.22
Week 2	69.06 <sup>a</sup> ±5.91	82.45 <sup>a</sup> ±6.18	67.06 <sup>b</sup> ±2.27	4.79 <sup>b</sup> ±0.5	7.55 <sup>a</sup> ±2.54	4.71 <sup>b</sup> ±0.07	0.85 <sup>a</sup> ±0.15	1.27 <sup>a</sup> ±0.63	0.66 <sup>a</sup> ±0.15
Week 3	63.63 <sup>b</sup> ±4.43	85.12 <sup>a</sup> ±0.449.47	65.75 <sup>b</sup> ±2.27	4.92 <sup>b</sup> ±0.36	6.55 <sup>a</sup> ±1.1	4.82 <sup>b</sup> ±0.54	0.9 <sup>a</sup> ±0.15	1.32 <sup>a</sup> ±0.07	0.74 <sup>a</sup> ±0.15
Week 4	61.58 <sup>b</sup> ±3.16	83.28 <sup>a</sup> ±2.83	64.82 <sup>b</sup> ±2.11	4.4 <sup>b</sup> ±0.62	6.82 <sup>a</sup> ±1.03	4.21 <sup>b</sup> ±0.46	1.1 <sup>a</sup> ±0.08	1.17 <sup>a</sup> ±0.25	0.92 <sup>a</sup> ±0.83
Week 5	63.93 <sup>b</sup> ±2.61	84.33 <sup>a</sup> ±0.56	65.45 <sup>b</sup> ±1.03	4.35 <sup>b</sup> ±0.61	7.13 <sup>a</sup> ±1.25	4.08 <sup>b</sup> ±0.33	1.03 <sup>a</sup> ±0.3	1.14 <sup>a</sup> ±0.33	0.9 <sup>a</sup> ±0.32

For each analyzed parameter: Means with different letters in each line and column- are significantly different (a versus b=p<0.05). Group 1: diabetic dogs receiving camel milk; Group 2: Diabetic dogs fed on cow milk; Group 3: Healthy dogs receiving camel milk; Day 0: The first day of the treatment with milk (after injection of alloxan)

**Table 2:** Weekly variations of total proteins, cholesterol and triglycerides (TG) levels in group 2 + camel milk (CM) and group 1 during the third test

	Total proteins (g/l)		Cholesterol (mmol/l)		TG (mmol/l)	
	Group 2+ CM	Group1	Group 2+ CM	Group 1	Group 2+CM	Group 1
Day 0	78.41 <sup>a</sup> ± 7.94	63.78 <sup>c</sup> ± 1.66	8.45 <sup>a</sup> ± 0.69	4.14 <sup>c</sup> ± 0.09	1.26 <sup>a</sup> ± 0.18	0.51 <sup>a</sup> ± 0.06
Week 1	75.68 <sup>a</sup> ± 7.15	61.61 <sup>c</sup> ± 1.28	7.47 <sup>a</sup> ± 0.27	5.51 <sup>c</sup> ± 0.91	1.44 <sup>a</sup> ± 0.15	0.77 <sup>a</sup> ± 0.12
Week 2	72.6 <sup>ab</sup> ± 5.97	62.69 <sup>c</sup> ± 3.3	6.94 <sup>ab</sup> ± 0.65	4.94 <sup>c</sup> ± 0.65	1.13 <sup>a</sup> ± 0.35	0.61 <sup>a</sup> ± 0.16
Week 3	71.78 <sup>ab</sup> ± 5.7	65.64 <sup>c</sup> ± 1.79	6.49 <sup>ab</sup> ± 1.01	5.45 <sup>c</sup> ± 0.36	1.14 <sup>a</sup> ± 0.02	0.95 <sup>a</sup> ± 0.18
Week 4	65.67 <sup>bc</sup> ± 8.3	60.77 <sup>c</sup> ± 2.59	5.33 <sup>bc</sup> ± 1.08	4.53 <sup>c</sup> ± 0.32	0.99 <sup>a</sup> ± 0.16	1.21 <sup>a</sup> ± 0.14
Week 5	64.51 <sup>c</sup> ± 12.01	69.18 <sup>c</sup> ± 0.79	5.92 <sup>c</sup> ± 2.24	4.8 <sup>c</sup> ± 0.01	1.15 <sup>a</sup> ± 0.09	1.02 <sup>a</sup> ± 0.06
Week 6	61.48 <sup>c</sup> ± 5.79	61.48 <sup>c</sup> ± 1.01	5.55 <sup>c</sup> ± 1.19	3.95 <sup>c</sup> ± 0.82	1.02 <sup>a</sup> ± 0.27	0.85 <sup>a</sup> ± 0.99
Week 7	60.48 <sup>c</sup> ± 6.64	61.93 <sup>c</sup> ± 1.48	6.65 <sup>c</sup> ± 0.41	4.76 <sup>c</sup> ± 0.78	1.15 <sup>a</sup> ± 0.01	0.91 <sup>a</sup> ± 0.24
Week 8	63.24 <sup>c</sup> ± 2.38	63.24 <sup>c</sup> ± 1.16	5.89 <sup>c</sup> ± 0.7	4.03 <sup>c</sup> ± 0.12	1.12 <sup>a</sup> ± 0.09	0.94 <sup>a</sup> ± 0.26

For each analyzed parameter: Means with different letters in each line and column- are significantly different (a versus b=p<0.05). Group 1: diabetic dogs receiving camel milk from the previous test; Group 2 + CM: group 2 from test 1 treated with camel milk, Day 0: the first of treatment with camel milk; Week 1 to week 5: Weeks of treatment with camel milk; Weeks 6 +7+8 after stopping camel milk.

Hypoglycemic effect of camel milk is significantly observed after 3 weeks of treatment illustrated by a non significant difference in comparison with the healthy group.

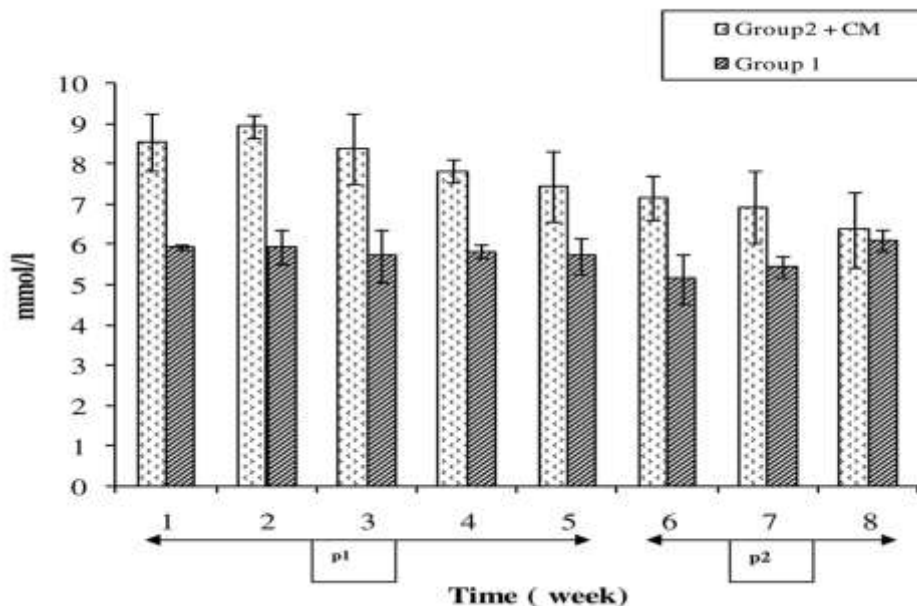
During the trial, diabetic dogs which receiving cow milk showed a high blood glucose level (8 mmol/l), an increase in cholesterol levels (from 5.99 ± 0.58 to 7.13 ± 1.25 mmol/l) and total proteins concentrations (from 79.18 ± 6.07 to 84.33 ± 0, 56 g/l) table 1. Triglycerides (TG) levels were not influenced by the diabetic status.

The healthy dogs (group 3), used as control, showed homogenous values of blood glucose levels as illustrated in figure 1 and constant levels for different parameters during the trial (table 1).

#### Intravenous Glucose Tolerance Test: IGTT

The results were illustrated in figure 2; the difference was mostly observed especially between group 2 and the two other groups.

Diabetic dogs treated with cow milk, showed a diabetic



**Fig. 3:** Weekly variations of blood glucose in (group 2 +camel milk) and group 1 during the third test. p1: period 1: During the treatment with camel milk; p 2: period 2: After stopping camel milk: 3 weeks; Group 1: Diabetic dogs treated in test period 1 with camel milk; Group 2 + CM: Diabetic dogs treated in test 1 with cow milk + insulin and received in this test (test 2) camel milk.

state confirmed by high levels of blood glucose before injection of glucose and a small decrease after 60 min. In group1 treated with camel milk, blood glucose level showed a decrease at 30 min and a stability of this state after 60 min (Fig. 2) after glucose challenge. A non significant effect was revealed in comparison with group 3 during the test.

### Test 2: Effect of camel milk in diabetic dogs treated previously with cow milk

When treated with camel milk, dogs from group 2 + CM showed a slow decrease in fast blood glucose levels (Fig. 3).

At week 4, blood glucose level showed a significant decrease (from  $9.83 \pm 0.72$  mmol/l before drinking milk to  $7.83 \pm 0.88$  mmol/l;  $p < 0.05$ ). A similar result was seen in total proteins (from  $78.41 \pm 7.94$  to  $65.67 \pm 8.3$  g/l) and in cholesterol concentrations (from  $8.45 \pm 0.69$  to  $5.33 \pm 1.08$  mmol/l) (Table 2).

However, this decline was slower than the one observed in the previous test (significant difference showed at week 3 in the first trial). In the last week of treatment (week 5) blood glucose level was about  $7.44 \pm 0.55$  mmol/l in (group 2 + CM) but it was only about  $5.66 \pm 0.16$  mmol/l in group 1 (first trial, Fig. 1). This blood glucose range was maintained after stopping milk (during the followed 3 weeks) and was accompanied with a normal range of total protein ( $61.86 \pm 1.54$ g/l) and cholesterol concentrations ( $6.01 \pm 1.02$  mmol/l) (Table 2).

Dogs from group 1 treated previously with camel milk (test 1) showed normal blood glucose levels (5.16 - 6.5 mmol/l;

Fig. 3), cholesterol (4.14-5.51 mmol/l), TG (0.51 -1.21 mmol/l) and total proteins concentrations (60.77- 69.18 g/l). (Table 2). This group (showing a healthy state) was used to follow glycemic control, lipids and proteins profile for a longer period (9 weeks) after stopping treatment with camel milk.

### Discussion

This study was conducted to evaluate the effect of camel milk on alloxan- induced diabetic dogs.

A single dose of alloxan injected to dogs was able to produce a reproducible model of diabetes mellitus that had minimal beta cell activity, and elevated glucose, total proteins and cholesterol levels. Alloxan injection caused a toxic effect on kidney and liver in addition to the pancreas as investigated by other study on alloxan induced- diabetes in dogs.<sup>13</sup>

Diabetes in dogs is generally associated, in addition to high blood glucose levels, with an increase of total proteins concentrations<sup>14</sup> which was illustrated in our study in all dogs after injection of alloxan and especially in dogs from group 2 treated with cow milk during the trial. This may be due to the toxicity of alloxan on the proximal convoluted renal tube.<sup>15</sup>

A significant decrease on blood glucose levels was well showed on dogs treated with camel milk. This decrease was statistically illustrated since week 3 by an improvement on glycemic control and a normal range of blood glucose levels

The stability of this glycemic state was shown by the end of the trial and was confirmed by intravenous glucose

tolerance test (IGTT). This stability of blood glucose levels was associated to a decline of total proteins and cholesterol concentrations and a steadiness of this state since week 3 and after stopping to drink camel milk.

This hypoglycemic effect of camel milk may be due to the high level of insulin in comparison to cow milk,<sup>16</sup> whereas in our assay, the results showed that it may not be due to this particularity factor because the efficacy of camel milk on glycemic control was observed also after stopping camel milk.

This therapeutic effect of camel milk was traditionally described as good in terms of glycemic control or anabolic effect.<sup>7, 17</sup> It may be explained by special properties of camel milk in comparison with milk from other species.<sup>18</sup>

Since blood glucose, proteins and lipids profiles were controlled by endocrine, paracrine and autocrine interactions; there might be more active principle in camel milk (peptides, vitamins, fatty acids...) than in bovine milk.<sup>19</sup> High mineral content (sodium, potassium, copper and magnesium) as well as a high vitamin C intake<sup>18,19</sup> may act as antioxidant thereby removing free radicals, which may provide an additional benefit to the animals treated with camel milk.<sup>20</sup> Camel milk may be able to eliminate the alloxan toxicity on pancreas or has a regenerative effect on beta cells and could be used as a curative treatment of diabetes in dogs.

As observed in the last test of this research, hypoglycemic effect of camel milk is slower when the animals were treated previously with cow milk. Some experiments suggested that cow milk proteins may be an environmental trigger for the development of diabetes in susceptible subjects and elevated levels of anti bovine serum albumin (BSA) antibodies was detected in diabetic animals and patient.<sup>20, 21</sup>

From the results presented in our study, a therapeutic efficacy of camel milk on alloxan-induced diabetic dogs was well shown. This may have an important implication for the clinical management of diabetes mellitus in humans. But further studies are warranted to fractionate the active principle and to find out its exact mode of action.

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