Research Article

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Biochemical Study of Induced Diabetes Mellitus by Experimental Total Pancreatectomy in Dogs

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Abstract

The objective of the current study was evaluating the status of blood serum biochemical parameters in poorly controlled diabetes mellitus induced after experimental total pancreatectomy in local crossbreeding dogs. The biochemical assay was taken before the surgical operation and on the last two days of the insulin treatment period and after termination of insulin therapy till death of animals due to ketoacidosis after detecting severe ketonuria on urinalysis by urine stripe test when insulin withdrawn. Results of estimating the various biochemical parameters revealed a significant increase in the blood serum level of liver enzymes [Alanine amino transaminase, alkaline phosphatase, and Aspartate amino transaminase], total cholesterol and potassium ions, while a significant decrease in chloride ions took place in both insulin treatment and withdrawal periods. On the other hand, significant increases in blood serum levels of triglyceride, total bilirubin, sodium ions, and blood urea nitrogen with significant decrease in total calcium was occurred in the insulin withdrawal period only. In conclusion, the first mentioned biochemical parameters might be involved in the pathogenesis of poorly controlled diabetes mellitus while the later mentioned parameters which exhibited significant changes only after cessation of insulin therapy might be involved in the pathogenesis of surgically induced diabetic ketoacidosis in dogs.

Keywords: Diabetes, Pancreatectomy, Parameters, Ketoacidosis.

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Introduction

To illustrate the advancement of diabetic changes in an animal model, the effects of experimental total pancreatectomy on serum biochemical features in dogs have been studied either with postoperative insulin administration which was discontinued (1) or with postoperative insulin injections which was insufficient to control resultant diabetes mellitus (DM) adequately post operation (2, 3) or without postoperative insulin therapy after DM induction (4, 5).

No study has described the multiple biochemical features of surgically induced poorly controlled experimental DM before and after stopping the treatment with insulin. The deterioration in potassium tolerance after pancreatectomy in dogs was determined (6-8). Pancreatogenous canine diabetes led to hypercholesterolemia with an insignificant rise in triglycerides (3). The chloride metabolism of dogs in diabetes after pancreatectomy was investigated (9). The lipid metabolism by determining lipoprotein (LP) fraction, triglyceride (TG), free fatty acid (FFA) and post heparin lipolytic activity (PHLA) in the blood of pancreatectomized dogs was described (1). It has been found that with more than 92% pancreatectomy alone, all the dogs developed diabetes immediately after the operation with an increase in the serum TG level (5). The serum lipoprotein patterns of normal and depancreatized dogs, with and without insulin treatment was determined (10).

Diabetic ketosis (DK) and diabetic ketoacidosis (DKA) are life-threatening complications of DM that are characterized by hyperglycemia glycosuria, and ketonuria (11). DKA is the most prominent and severe complication of DM in dog and cats due to the poor management of insulin treatment (12). The outcome of 127 dogs with diabetic ketoacidosis (DKA), many of the dogs formerly treated with insulin are treated insufficiently either by administering the insulin only once a day or by giving inadequate dosage of insulin (< 0.5 U/kg) which may have participated in the evolution of DKA in these dogs, also insufficient insulin treatment is linked with increased danger of DKA in humans with previously diagnosed DM (13).

In previous study, acid-base and hormonal abnormalities in dogs with naturally occurring diabetes mellitus (high blood glucose, Alkaline phosphatase (ALP), Alanine transaminase (ALT), cholesterol levels) might be indicators of a poor pretreatment prognosis (14). Parameters are more accurately discriminate between animals which survive or not survive the stabilization period with little overlap between the values obtained in survivors and non-survivors (14).

In the insights of the above information, the objective of the current study was to characterize the changes in multiple biochemical features during the insulin treatment and insulin withdrawal periods of poorly controlled experimental DM induced by total pancreatectomy in local crossbreeding dogs in order to have some

information about the margin of safety that these pancreatectomized dogs own between persistent hyperglycemia and DKA.

Materials and Methods

Preoperative procedures

The experiments were approved by the ethics committee at the College of Veterinary Medicine, University of Duhok/ Iraq (Reference No.: CVM20180910UD in 01-09-2018). Five normal adult female local crossbreeding dogs were used in the current biochemical study. The body weights of the animals were extended from 17.5 to 27.7 kg at mean of 20.88 kg on pancreatectomy operation day. They were kept in individual cages, maintained on a high protein diet (minced beef 500g/animal/day) and tap water in estimated quantities to determine the amount of water consumed per day. Ten grams of pancreatic enzymes powder (Zoetis, United Kingdom) was added to the diet.

Surgical Technique

The dogs were pre-medicated with atropine (ATROVAP, VAPCO, Jordan) at a dose of 0.04mg/kg B. Wt., and after 10 minutes, the induction and maintenance of general anesthesia was accomplished by mixture of Xylazine and Ketamine as used by Kim *et al.* (15) except that the mixture was injected intramuscularly not intravenously. The dose of Xylazine (Xylanit, Nita-farm, Russia) was 2mg/kg B. Wt., and of Ketamine (KETAMIN, Dutch Farm, Holland) was15mg/kg B. Wt. Experimental total pancreatectomy without duodenectomy where the shared pancreaticoduodenal arterial arcade removed with the pancreas was performed. The pancreaticoduodenal arcade is the anastomosis of the superior and inferior pancreaticoduodenal arteries and is embedded in the substance of the pancreatic head and supplies both pancreas and duodenum. So, the evolved technique disrupted the vascular integrity of the duodenum. Excision of the pancreaticoduodenal vascular arcade results in a devascularized but viable duodenal loop (16).

Postoperative Care

All pancreatectomized dogs were yielded to daily observation for 14 – 60 days to check their general condition (Table 1). The dogs were weighed weekly. They treated with 20 to 30 units of human recombinant insulin (Mixtard® 30 Novo Nordisk/Denmark) (17) by injection sub cut before feeding once daily that prevented the appearance of ketone bodies in the urine and to initiate a poorly controlled diabetic state (one daily fasting blood glucose level was ranging from 350 – 650 mg/dl). They were returned to the preoperative feeding at one week after surgery. On this regimen, the dogs lost weight slowly. However, ate well and their wounds healed without incident. Dose of insulin was determined based on daily fasting blood glucose measures by glucometer.

Serum Biochemistry

Blood specimens (5ml) was collected from the cephalic vein afternoon post-fasting for about 24 h to measure the levels of aspartate transaminase (AST), ALT, ALP, total cholesterol, triglyceride, total bilirubin,

glucose, blood urea nitrogen (BUN), creatinine, sodium ions (Na+), potassium ions (K+), total calcium, chloride ions (Cl^-), and phosphorus in serum. Cobbas 6000 Chemistry Analyzer / Roche/ Germany used to estimate the above serum biochemical indices. Serum chemical examination was performed in one week before operation (preoperative period). This biochemical investigation was repeated in the last two days of insulin injection (insulin treatment period) and continued every day after stopping the injection of insulin until death of animals (insulin withdrawal period).

Urinalysis

Urine reagents stripe test is used to detect glucose and ketone bodies in the urine of dogs and cats (18, 19). The stripe contains reagents for many chemicals including glucose and acetoacetate. The test was performed by dipping the stripe in urine sample to check for glycosuria and ketonuria before operation and in the last two days of insulin therapy (insulin treatment period) and in most days after stopping insulin injections until death of animals (insulin withdrawal period).

Table (1): The observation periods from operation day and survival times after discontinuation of insulin in pancreatectomized dogs

Dog No.	Days of observation during insulin treatment	Survival days after insulin withdrawal
1	60 days	5 days
2	32 days	10 days
3	30 days	8 days
4	34 days	9 days
5	14 days	7 days

Statistical analysis

Before evaluating the biochemical data statistically, they were assured for similarity and analogy of variance by means of residual plots and Bartlett's test, successively. The statistics were analyzed using logistic regression in GenStat 16th Edition. ANOVA test and multiple comparisons were used to locate the diversity of variables between the three periods of the study. All the values of biochemical estimations were expressed as mean ± standard error of mean (SEM). Values ($P<0.05$) were considered significant.

Results

Generally, the dogs were not clinically ill. All animals exhibited marked diabetic signs of polyuria and polydipsia after pancreatectomy. Despite consuming all diet given to these dogs, dogs were wasting clearly and manifesting an obvious decrement in the weight of the body from 18.3 – 64.7% of preoperative estimates.

After observation for 14–60 days, all dogs were sacrificed by withdrawing insulin therapy. Without insulin, depancreatized animals died in severe diabetic ketoacidosis within 5, 7, 8, 9, and 10 days. All animals suffered from vomiting, dehydration and lethargy before death. After death, yellow discoloration observed at autopsy indicating fatty liver development.

Urinalysis revealed glycosuria in the last two days of insulin treatment period. Ketone body-positive reaction (ketonuria) beside glycosuria during the insulin withdrawal period were detected in urine stripe test which was always found to be considerable (+++ ve) and unchangeable.

The permanent DM clinical alterations were associated with several variations in serum biochemical parameters. The analyses revealed clear cut and often dramatic biochemical alterations. After pancreatectomy and fasting hyperglycemia, there was consistent elevation for serum ALP, ALT, AST activities, and a significant gradual increase in total cholesterol and K+ concentrations after induction of diabetes compared with the preoperative values. On the other hand, there is a significant decrease in chloride ions (Cl^-) concentrations after operation compared with the values before pancreatectomy (Table 2)

A triglyceride, total bilirubin, Na +, and BUN concentrations remained unchanged significantly during insulin treatment period in comparison with their levels before the operation and then exaggerated significantly and excessively during insulin withdrawal period. In opposite to that, the serum total calcium concentration decreased significantly below the preoperative level after insulin withdrawal (Table 2).

There were no significant variations in serum phosphorus and creatinine levels in all three periods of the study. Slight increases in phosphorus and slight decrease in creatinine from those of preoperative values were recorded (Table 2).

Table (2) Serum biochemical profile in the pancreatectomized dogs (n=5)

No.	Parameter	Unit	Before pancreatectomy (Mean ±SEM)	After pancreatectomy with insulin (Mean ±SEM)	After pancreatectomy without insulin (Mean ± SEM)
1	Glucose	mg/dl	98.9 ± 50.6	420.7 ± 36.7 ***	520.8 ± 48.2 ***
2	ALT	IU/L	28.1 ± 17.9	96.0 ± 16.4 ***	113.9 ± 16.9 ***
3	ALP	IU/L	94.7 ± 37.4	184.7 ± 34.3 **	289.4 ± 35.3 ***
4	AST	IU/L	25.7 ± 20.2	51.6 ± 12.7 ***	74.4 ± 20.6 ***
5	Bilirubin (Total)	mg/dl	0.23 ± 0.29	0.31 ± 0.22	0.77 ± 0.28 ***
6	Triglyceride	mg/dl	54.5 ± 159.9	93.9 ± 142.4	518.9 ± 162.4 ***
7	Cholesterol (Total)	mg/dl	206.2 ± 25.2	263.2 ± 19.1 **	286.4 ± 24.2 ***
8	BUN	mg/dl	32.6 ± 13.7	39.3 ± 11.9	66.8 ± 12.6 **
9	Creatinine	mg/dl	0.83 ± 0.18	0.76 ± 0.17	0.76 ± 0.11
10	K +	mmol/L	4.14 ± 0.24	5.37 ± 0.21 ***	4.94 ± 0.25 ***
11	Na +	mmol/L	138.1 ± 3.09	140.2 ± 2.96	146.7 ± 3.14 **
12	Cl^-	mmol/L	107.9 ± 3.22	98.7 ± 3.22 ***	98.9 ± 3.24 ***
13	Phosphorus	mg/dl	3.48 ± 1.18	3.85 ± 0.16	3.79 ± 0.18
14	Calcium (Total)	mg/dl	10.7 ± 0.230	10.65 ± 0.233	8.68 ± 0.233 ***

Significance in comparison with values before pancreatectomy * P < 0.05, ** P < 0.01, *** P < 0.001

Discussions

All animals in the current study demonstrated ideal signs like the spontaneous DM in dogs. The identification of DM in canine depends upon the existence of polyuria, polydipsia, polyphagia and weight loss with concurrent hyperglycemia and glycosuria (20, 21). Canine DM progresses from profound hyperglycemia to life-threatening DKA and affected dogs will die without insulin therapy due to severe insulin deficiency at the time of diagnosis (22). All animals in the present study suffered from fatal DKA after insulin withdrawal as indicated by ketonuria on urine stripe test. Canine DKA is ordinarily diagnosed through ketonuria by measuring the urinary acetoacetate (23).

In present study, surgically induced DM caused considerable increases in ALT, AST, and ALP and bilirubin which were highly intensified in contrast to their activities before the operation. These changes were accompanied by yellow discoloration of liver at post mortem. Previous study which observed fatty degeneration in the liver post pancreatectomy in the poor control diabetic dogs (2). Liver fatty degeneration was manifested by elevated activities of the above-mentioned liver enzymes (2). Study of experimental total pancreatectomy in dogs, revealed yellow discoloration of the liver and increases in serum ALP and ALT activities, and bilirubin concentrations (direct and indirect) were exaggerated (4). All changes were signal for diffuse damage of hepatic cells; also, generalized fatty metamorphosis was shown in histopathologic examination (4). Histopathologic examination in spontaneous canine DM indicated fatty deposition in the liver (24). In comparison to human, slight elevation in plasma bilirubin level in animals are considerable signal of liver injury (25). In a recent study, the progressively increased activities of AST, ALT, ALP, and Bilirubin was attributed to the oxidative stress to the liver which leads to producing the free radicals that cause leakage of these enzymes to the blood circulation as a result of increased permeability of cell wall (26).

Hypercholesterolemia and hypertriglyceridemia are common in diabetes in dogs (20). The mean value of serum triglyceride was highly elevated ($P<0.001$) after insulin withdrawal in comparison with its level before operation (Table 2). Elevation of triglyceride was less severe in the dogs of subtotal pancreatectomy than in those which were totally pancreatectomized (1). Thereafter, the totally depancreatized dogs were died within 7 days after ceasing insulin treatment, and a marked deposition of fat in the hepatic cells noticed histologically in those animals. The mean value of serum total cholesterol was highly elevated ($P<0.01$) during insulin treatment period and was further elevated ($P<0.001$) after insulin withdrawal in comparison with its level before operation (Table 2). Rising in total cholesterol levels was detected after induction of diabetes chemically by alloxan in rabbits (27) and dogs (28). Increases in blood cholesterol level were also reported earlier in experimental as well as spontaneous canine DM (29).

In the present study, severe hypochloremia ($p<0.001$) was observed after induction of diabetes post pancreatectomy. One possible reason for the Cl^- declining is the excessive urinary loss caused by the osmotic diuresis induced by glycosuria (30). The current study showed severe dropping in total calcium level ($p<0.001$) in the insulin withdrawal period. There is great agreement between the results of the present study and those of previous study (31). It has been found that lipemia (hypertriglyceridemia and hypercholesterolemia), hypochloremia, hypocalcemia, and high hepatic enzyme activities were the most frequently identified serum biochemical abnormalities in diabetic dogs (31). Survival of dogs suffering from DKA was correlated with the degree of anemia, hypocalcemia, and acidosis due to base deficit (13).

The current study revealed a significant rising ($P<0.01$) in the mean value of BUN (66.8 ± 12.6 mg/dl) in the insulin withdrawal period. Because all animals in the current study were non-survivors, this finding is agreement with previous study in their retrospective survey of 43 dogs with DM (32). It has been found that dogs suffering from DM were non-survivors if blood glucose was exceeded 450mg/dl, ALP above 540 IU/L, ALT higher than 175 IU/L, and blood urea was more than 25.2mg/dl or cholesterol was beyond 657.9mg/dl.

In the present study, there was a significant rising ($P<0.01$) in Na+ level after stopping insulin therapy. This rising was accompanied by severe lipemia in which serum gave milky appearance. Severe lipemia might appear to elevate the serum sodium value as lipemia dislodges sodium into the non-lipemic proportion of serum, making a normal serum sodium level seem increased (33).

In the present study, there was significant elevation ($P<0.001$) in serum K+ level after pancreatectomy. This elevation might be ascribed to insulin deficiency due to poor controlled diabetic state during insulin treatment period and insulin withdrawal period. Pancreatectomy in dogs led to a marked deterioration in potassium tolerance and lethal cardiac toxicity (6-8). It has been found that when depancreatized dogs were provided by exogenous insulin, potassium tolerance was returned to normal (6). Insulin therapy returns the serum potassium concentration to normal state by treating the insulin deficiency and hyperosmolality, empowering transferring of the potassium to inside the cells and reducing the requirement for protein catabolism (34).

The Mean ± SE values for creatinine before operation and in diabetic dogs during insulin therapy and after termination of therapy were 0.833±0.187 mg/dl, 0.767±0.171mg/dl and 0.766±0.108mg/dl, respectively (Table 2). There was no significant difference in the creatinine values between the three periods of the experiment. This finding is in agreement with previous studies (24, 35).

Serum phosphorus level did not change significantly in all three periods of the present study. Serum phosphorus concentrations might be decreased or normal or increased, depending on the duration of illness and kidney function. Most dogs and cats with DKA have either normal or decreased serum phosphorus concentrations

on pretreatment testing (36). Dehydration and decreased phosphorus excretion in the later stages of the disease might cause the serum phosphorous concentration to be normal or increased (34).

Conclusions

In conclusion: Triglyceride, total bilirubin, Na+, total calcium, and BUN might be involved in the pathogenesis of surgically-induced canine DKA. Whereas ALT, ALP, AST, total cholesterol, K+ and Cl^- might be involved in the pathogenesis of uncontrolled DM in dogs. The surgically induced diabetes mellitus by experimental total pancreatectomy in the local crossbreeding dogs was a beneficial model to examine the series of progression of the disease through incorporating the clinical examination to the biochemical results.

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دراسة كيميائية حيوية للداء السكري المستحث باستئصال البنكرياس الكامل في الكلاب الهجينة المحلية

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الخلاصة

الهدف من هذه الدراسة كان تقييم حالة الأوساط الكيميائية الحيوية لمصل الدم في حالة سوء السيطرة على الداء السكري في الكلاب الهجينة المحلية والمستحث بعد استئصال البنكرياس الكامل الاختباري. أخذت المقايسة الكيميائية الحيوية قبل العملية الجراحية وخلال اليومين الأخيرين من فترة العلاج بالأنسولين وبعد إنهاء المعالجة بالأنسولين لحين نفوق الحيوانات بسبب أصابتها بالحماض الكيتوني السكري بعد الكشف عن بول الكيتوني شديد عند تحليل البول باستعمال فحص شريط البول بعد ايقاف العلاج بالأنسولين. كشفت نتائج تقدير الأوساط الكيميائية الحيوية المتنوعة عن حصول إزديادات معتد بها لمستويات مصل الدم من أنزيمات الكبد {الترانساميناز الأميني لحمض الالناين، الفوسفاتاز القلوي، والترانساميناز الأميني لملح حمض الأسبارتيك} والكولسترول الكلي وأيونات البوتاسيوم، بينما حصل انخفاض معتد به لمستوى مصل الدم من أيونات الكلوريد في فترة العلاج بالأنسولين وكذلك خلال فترة انقطاع الأنسولين. من جانب آخر ظهرت إزديادات معتد بها في مستويات مصل الدم من ثلاثي الغليسريد والبليروبن الكلي وأيونات الصوديوم ونيتروجين يوريا الدم مع انخفاض معتد به للكلسيوم الكلي في فترة انقطاع الانسولين فقط. بالاستنتاج فأن الأوساط الكيميائية الحيوية المذكورة أولا قد تكون مشاركة في اعتلال سوء السيطرة على الداء السكري بينما الأوساط المذكورة آخرا وهي التي عرضت تغييرات معتد بها فقط بعد وقف العلاج بالأنسولين قد تكون مشاركة في اعتلال الحماض الكيتوني السكري المستحث جراحيا في الكلاب.

الكلمات المفتاحية: الكلاب الهجينة، داء السكري، استئصال البنكرياس، الأوساط، الحماض الكيتوني السكري.