Abnormal renovascular resistance in dogs with diabetes mellitus: correlation with glycemic status and proteinuria

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Summary

Present study was conducted with the objectives of determining the renal vascular resistance in dogs with diabetes mellitus and to study the correlation between the indices of renovascular resistance with glycemic status, systolic blood pressure (SBP) and proteinuria in dogs with diabetes mellitus. This study was conducted on seventeen diabetic dogs and ten apparently healthy dogs. Increased renal resistive index (RI) and pulsatility index (PI) were observed in diabetic dogs as compared to healthy dogs. Systemic hypertension and proteinuria were observed in 10 and 3 out of 17 diabetic dogs, respectively. Significant positive correlation was observed between the indices of renovascular resistance and fasting blood glucose levels and between the indices of renovascular resistance and serum glycated hemoglobin levels. No correlation was observed between the indices of renovascular resistance and SBP as well as the indices of renovascular resistance and proteinuria. As the indices of renovascular resistance correlate significantly with glycemic status, they can be used as the early marker for kidney damage in diabetic patients. Among these indices renal PI was found to be more sensitive than renal RI.

Key words: Diabetes mellitus, Dog, Glycemic status, Proteinuria, Renovascular resistance

Introduction

Diabetes mellitus is a relatively common endocrine disorder occurring mostly in middle aged and older dogs (Hoenig, 2002; Davison *et al*., 2005). It results in numerous vascular complications like vasculopathy, systemic hypertension, nephropathy, etc (Herring *et al*., 2014). These complications significantly contribute to morbidity and mortality in human diabetic patients (Herring *et al*., 2014). Owing to shorter life span and sporadic nature of the disease, these complications are less frequently reported in canine diabetic patients (Munana, 1995). Considerable advances in veterinary medicine have enabled the veterinarians and pet owners to effectively manage diabetes in dogs. This has led to the increased life span of diabetic dogs. Due to this there is a possibility of increased occurrence of these complications in diabetic dogs (Munana, 1995).

Systemic hypertension occurs in insulin dependent diabetes mellitus as a result of arteriosclerosis and increased peripheral vascular resistance (Littman, 2000; Cruickshank *et al*., 2002). Systemic hypertension was found in about 46 percent of diabetic dogs (Struble *et al*., 1998). It plays an important role in the development and progression of diabetic nephropathy in human beings (Patel, 2007). Loss of renal auto regulation in hypertensive diabetic patients leads to glomerular hypertension and diabetic nephropathy (Hayashi *et al*., 1992). Diabetic nephropathy is observed in 40 to 50% of human insulin dependent diabetes mellitus patients and two thirds of these patients will develop end stage renal disease (Munana, 1995). Although there are no reports on the prevalence of diabetic nephropathy in canine diabetes mellitus, histopathological lesions of diabetic nephropathy are described in experimentally induced cases of canine diabetes mellitus (Gaber *et al*., 1994). Azotemia, the marker of renal injury is observed only after 75 to 80% of nephron are damaged (Feldmann and Ettinger, 2005; Novellas *et al*., 2007).

Renal cortical vasoconstriction with resultant increase in renal arterial resistance is the earliest change noticed in nephropathy (Colli *et al*., 1993). This can be detected by studying doppler waveforms from renal vasculature (Novellas *et al*., 2008). Resistive index (RI) and pulsatility index (PI) calculated from renal blood vessels are the widely accepted indicators of renal vascular resistance (Novellas *et al*., 2008). Renal RI and PI correlate with the severity and progression of renal injury and they are used as early markers for end organ damage in kidneys (Novellas *et al*., 2008). Studies indicated that renal RI and PI correlate with systolic blood pressure (SBP), glycemic status and duration of diabetes in human beings (Ishimura *et al*., 1997; Sari *et al*., 1999). Renal RI and PI are used for early detection of renal injury and also as survival indicators in human diabetic patients (Casadei *et al*., 2000).

Studies exploring the status of renovascular resistance in canine diabetic patients are limited. Till now, only one study has been conducted involving only three diabetic dogs (Novellas *et al*., 2008). Detailed studies exploring the possible correlation between the indices of renovascular resistance to SBP, proteinuria

and glycemic status are lacking. With this background, the present study was conducted with the objectives of determining the renal vascular resistance in dogs with diabetes mellitus and to study the correlation between SBP, proteinuria and glycemic status with renal vascular resistance in dogs with diabetes mellitus.

Materials and Methods

Present study was conducted at the Teaching Hospital, Madras Veterinary College, Chennai, Tamil Nadu, India. Seventeen diabetic dogs and 10 apparently healthy dogs were selected for the present study. All these animals were subjected to physical examination, haematological examination (haemoglobin, total erythrocyte count, total leukocyte count, packed cell volume, platelet count and differential cell count), biochemical analysis (blood urea nitrogen, creatinine, total bilirubin, direct bilirubin, total protein, albumin, globulin, alanine amino transferase (ALT), alkaline phosphatase, cholesterol, triglycerides, glucose and glycated haemoglobin (HbA1c)), complete abdominal ultrasound and urinalysis. Confirmatory diagnosis of diabetes mellitus was made based on serial fasting blood glucose measurements, glycated haemoglobin measurements and Benedict's test.

Blood pressure measurement

Systolic blood pressure measurement was done before the other interventions according to the method described by Acierno and Labato (2005). Doppler ultrasound method of blood pressure measurement was carried out by using Vet-Dop doppler ultrasound blood pressure machine manufactured by Vmed Technology. The measurement was carried out at superficial palmar arterial arch by placing the animal in left lateral recumbency. Mean of the three measurements was taken as the reading. Dogs showing SBP of greater than 150 mmHg on a minimum of three different visits were declared as hypertensive. Based on the SBP, hypertensive dogs were categorized into mild hypertension if SBP is between 150-160 mmHg, moderate hypertension if SBP is between 161-180 mmHg and severe hypertension if SBP is greater than 180 mmHg (Novellas *et al*., 2007).

Determination of renal RI and PI

Triplex doppler ultrasonography was performed to determine the renal RI and PI by using ALOKA SSD 3500 ultrasound machine as per the procedure given by Novellas *et al*. (2009). Hair over the entire abdomen was clipped including the midway up the body wall over the right and left caudal intercostal spaces and liberal amount of acoustic gel was applied to the skin. The animals were fasted for 12 h and were in right or left lateral recumbency to scan the nondependent kidney. Different transducers and frequencies (3.8 MHz, 5 MHz and 7.5 MHz) were used depending on animal weight and renal depth. Color doppler was used to visualize the intrarenal vasculature. Subsequent pulsed doppler interrogation from one of the arteries was obtained with a sample width of 1.5-4 mm and a frequency of 4-7 MHz. The smallest scale that displayed the flow without aliasing was selected. Resistive and pulsatility index were calculated automatically by the software of the machine after manually entering peak systolic velocity, end diastolic velocity and time average maximum velocity (TMAX). The mean RI and PI for each kidney were determined by averaging a total of nine doppler waveforms from the interlobar or arcuate arteries at three separate locations (cranial pole, mid-portion, and caudal pole, three waveforms at each) (Fig. 1). Following formulae were used to calculate RI and PI:

$$RI = \frac{(\text{Peak systolic velocity}) - (\text{End diastolic velocity})}{\text{Peak systolic velocity}}$$

$$PI = \frac{(\text{Peak systolic velocity}) - (\text{End diastolic velocity})}{\text{TMAX}}$$

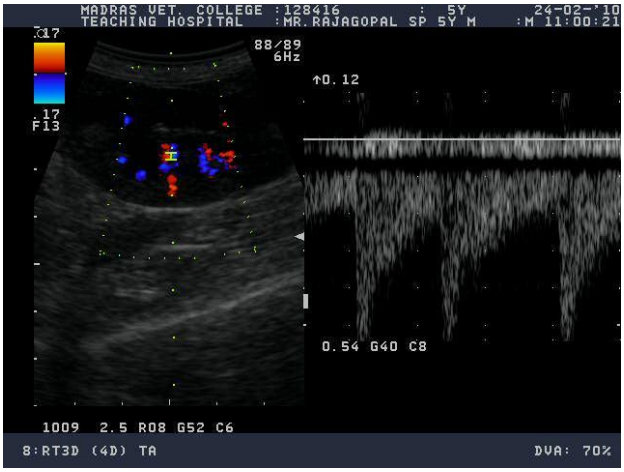

Fig. 1: Doppler ultrasound image showing the calculation of renal resistive index (RI) and pulsatility index (PI) at mid pole of kidney in a diabetic dog

Renal RI greater than 0.72 and renal PI greater than 1.52 was considered as increased (Novellas *et al*., 2007).

Statistical analysis

Resistive and pulsatility indices as well as SBP were compared between diabetic and control groups using two independent samples t-test. Correlation between fasting blood glucose and glycated hemoglobin with renovascular resistance indices were determined by Pearson's correlation. Data was subjected to statistical methods using SPSS software 16th version. A two tailed P-value less than 0.05 was considered as statistically significant.

Results

Among these 17 diabetic dogs, 13 were female and 4 were male belonging to different breeds (6 Labrador retriever, 4 Pomeranian, 3 non descript, 2 Doberman, and 2 German shepherd) with a mean age of 6.52 years (range 1.5 to 9 years). Polyuria, polydipsia, polyphagia

were the major clinical findings observed. Elevated alkaline phosphatase enzyme levels, hyper-cholesterolemia, hyperglycemia, elevated glycated hemoglobin levels, mild proteinuria and glycosuria were the abnormalities noticed. All the seventeen dogs were treated with a commercial human recombinant protamine zinc insulin formulation[@] 0.5 IU/kg, SC, once daily, before the meal. Constant monitoring was done till mild hyperglycemic state (i.e. about 130-140 mg/dl) was achieved and owners were advised to follow the medication. Precautions regarding medication, diet and regular review were also advised to owners.

Among 17 diabetic dogs, mild (n=3) to moderate (n=7) hypertension was noticed in 10 dogs (58.82%) (Table 1). Mean SBP was high in diabetic dogs as compared to healthy control (Fig. 2 and Table 2). Among these 10 hypertensive dogs, increased renal RI and PI was observed in 6 and 7 hypertensive diabetic dogs, respectively (Table 1). Systolic blood pressure neither correlated with any of the parameters of glycemic status nor with any of the indices of renovascular resistance in diabetic dogs (Table 3).

Mean renal RI ($P<0.05$) and PI ($P<0.01$) were significantly higher in diabetic dogs as compared to healthy dogs (Table 2, Figs. 3 and 4). Increased renal RI and PI were observed in 9 and 11 diabetic dogs, respectively (Table 1). Renal RI correlated highly significantly ($P<0.01$) with both fasting blood glucose levels and glycated hemoglobin levels. Similarly, statistically highly significant ($P<0.01$) correlation was noticed between renal PI and fasting blood glucose levels and renal PI and glycated hemoglobin levels (Table 3).

Mild proteinuria was observed in three (17.65%) diabetic dogs (Table 1). Among these three proteinuric diabetic dogs, renal RI was increased in two dogs and renal PI was increased in all the three dogs (Table 1). No correlation was observed between urine protein creatinine ratio (UPC) and SBP, UPC and fasting blood glucose levels, UPC and glycated hemoglobin levels and UPC and the indices of renovascular resistance (Table 3).

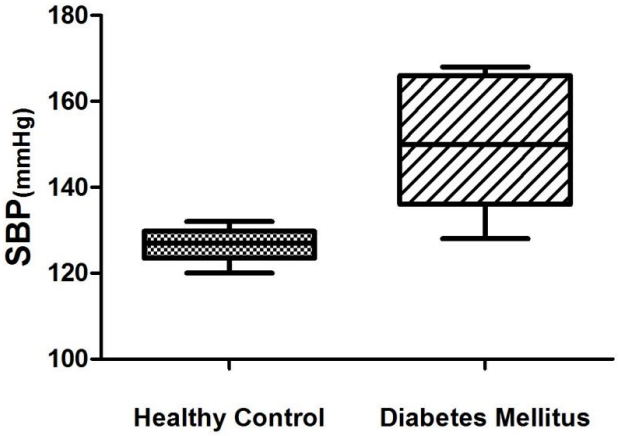

Fig. 2: Whisker-plot of systolic blood pressure (SBP) distribution in diabetic and healthy dogs

Table 1: Mean RI, mean PI, SBP, fasting blood glucose levels, glycated hemoglobin levels and UPC ratio in dogs with diabetes mellitus

Parameters	Dog																
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Mean RI	0.72	0.81	0.68	0.71	0.78	0.7	0.84	0.73	0.66	0.78	0.82	0.83	0.76	0.8	0.7	0.62	0.69
Mean PI	1.81	1.92	1.21	1.68	1.78	1.38	1.81	1.79	1.26	1.82	1.84	1.85	1.62	1.58	1.39	1.31	1.34
SBP mmHg	144	166	128	168	136	130	138	162	160	128	164	150	168	168	166	150	136
Fasting blood glucose levels (mg/dl)	522	572	468	525	572	425	582	578	429	570	620	634	454	574	490	399	430
Glycated hemoglobin (%)	10.9	11	9.4	10.8	10.9	10.3	11.8	11	9.3	11.2	11.8	11.9	10.6	10.4	9.4	9.6	10.2
UPC ratio	1.5	0.4	0.4	0.3	0.3	0.4	0.2	0.6	0.2	0.2	1.4	0.8	1.1	0.9	0.4	0.7	0

RI: Resistive index, PI: Pulsatility index, SBP: Systolic blood pressure, and UPC: Urine protein creatinine

Table 2: Mean±SE values of SBP, RI and PI in diabetic and healthy dogs

Parameters	Diabetic dogs		Healthy control	
	Mean	SE	Mean	SE
SBP (mmHg)	150.70**	3.76	126.70**	1.24
RI	0.74**	0.01	0.68**	0.01
PI	1.61**	0.05	1.23**	0.01

SBP: Systolic blood pressure, RI: Resistive index, and PI: Pulsatility index. ** $P<0.01$

Table 3: Pearson's correlation of glycemic status, SBP, RI and PI in diabetic dogs

	Fasting blood glucose	Glycated haemoglobin	UPC	SBP	RI	PI
Fasting blood glucose	1	0.82**	0.25	0.17	0.87**	0.86**
Glycated haemoglobin	-	1	0.29	0.00	0.85**	0.90**
UPC	-	-	1	0.36	0.22	0.33
SBP	-	-	-	1	0.11	0.18
RI	-	-	-	-	1	0.81**
PI	-	-	-	-	-	1

SBP: Systolic blood pressure, RI: Resistive index, and PI: Pulsatility index. ** Correlation is significant at the 0.01 level (2-tailed)

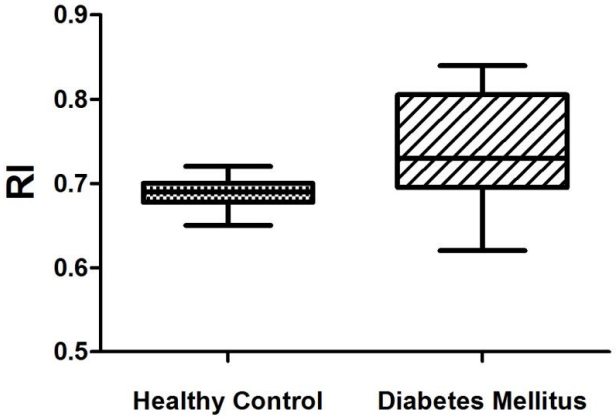

Fig. 3: Whisker-plot of renal resistive index (RI) distribution in diabetic and healthy dogs

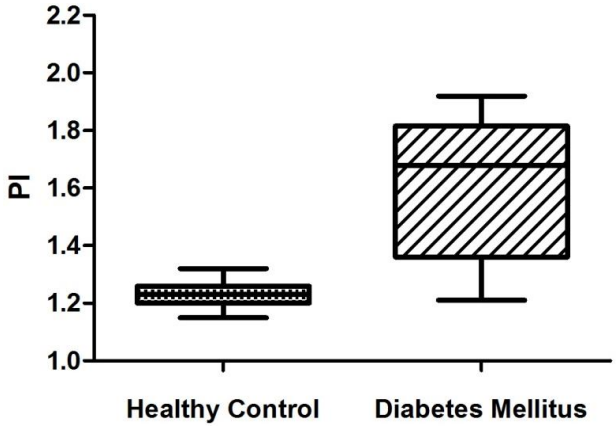

Fig. 4: Whisker-plot of renal pulsatility index (PI) distribution in diabetic and healthy dogs

Discussion

Diabetes mellitus is known to cause secondary hypertension in dogs (Littmann, 2000; Brown *et al*., 2007). In present study, hypertension was observed in 58.82% of diabetic dogs. This finding is supported by earlier studies. Struble *et al*. (1998) found hypertension in 45% of diabetic dogs and Herring *et al*. (2014) recorded systolic hypertension in 55% of diabetic dogs. Disturbed lipid metabolism leading to reduced vascular compliance, generalized glomerular hyperfilteration, increased peripheral vascular resistance and vasculopathy, etc will contribute to the development of hypertension in diabetic dogs (Dukes, 1992; Kraft and Egner, 2003). In present study, SBP ranged from 120-132 mmHg in healthy dogs and 128-168 mmHg in diabetic dogs (Fig. 2). This is supported by Herring *et al*. (2014), they also observed mild to moderate hypertension in most of the diabetic dogs. Few of the hypertensive diabetic dogs had increased values of renal RI and PI. This is supported by the observations of Novellas *et al*. (2007), who also observed increased renal RI and PI in few canine patients suffering from hepatic disease with elevated SBP.

Absence of correlation between SBP and glycemic status in this study, indicate that systemic hypertension might occur independently of glycemic status in diabetic dogs. However, there is paucity of information indicating the association between glycemic status and SBP in diabetic dogs. No studies have been conducted to elucidate the role of glycemic status in the development of hypertension in diabetic dogs. In present study, no correlation was observed between SBP and the indices of renovascular resistance. This is supported by the findings of Novellas *et al*. (2007). They did not observe any correlation between SBP and the indices of renovascular resistance in dogs, either.

Statistically significant increase in the values of renal RI ($P<0.05$) and PI ($P<0.01$) were noticed in diabetic dogs as compared to healthy dogs (Table 2, Figs. 3 and 4). This indicates the presence of renovascular resistance in diabetic dogs. Increased glycation of proteins due to hyperglycemia leads to arterial stiffness (Cruickshank *et al*., 2002). This increased arterial stiffness might reduce diastolic blood flow causing increased RI and PI. In contrast to our findings, Novellas *et al*. (2008) did not observe any rise in the values of renal RI and PI in diabetic dogs. However, study conducted by Novellas *et al*. (2008) involved only 3 diabetic dogs and they further suggested conducting studies exploring renovascular resistance in large population of diabetic dogs.

Highly significant correlation was noticed between fasting blood glucose levels and renal RI and fasting blood glucose levels and renal PI. This finding is supported by Novellas *et al*. (2008) and Youssef and Fawzy (2012). They observed significant positive correlation between blood glucose level and the indices of renovascular resistance in diabetic dogs and human beings, respectively. Highly significant positive correlation was also noticed between glycated hemoglobin levels and renal RI and glycated hemoglobin levels and renal PI. This finding is in concurrence with Santha *et al*. (2017), who also observed strong positive correlation between HbA1c and renal RI in human patients with diabetes mellitus. As serum glucose level is affected by various other factors, HbA1c is used as the stable marker of glycemic status in routine clinical practice (Miller, 1995). Hyperglycemia increases renal vascular resistance by activating intrarenal renin-angiotensin system and stimulating the local production of angiotensin II (Arima and Ito, 2003).

Presence of mild proteinuria in 17.65% of diabetic dogs in present study is supported by Herring *et al*. (2014), they observed proteinuria in 55% of diabetic dogs. Chronic hyperglycemia causes renal damage by glycosylating the glomerular proteins and finally leads to progressive renal failure by damaging various cell types of the kidney (Heilig *et al*., 1995; Lin *et al*., 2006; Fioretto and Mauer, 2007). Absence of correlation between UPC and the indices of renovascular resistance in present study is supported by earlier workers (Rivers *et al*., 1997; Koenhemsi *et al*., 2016). They also did not observe any correlation between proteinuria and the indices of renovascular resistance. Increase in renal RI in two of three proteinuric diabetic dogs and increase in renal PI in all the three proteinuric diabetic dogs is

supported by Koenhemsi *et al*. (2016). In their study they found that all the four proteinuric dogs had high renal PI values and renal RI was increased in only two proteinuric dogs. As renal PI considers the mean velocity within one cycle, therefore, it is a more sensitive marker of renovascular resistance than renal RI (Novellas *et al*., 2008).

Absence of correlation between UPC and SBP is supported by Hung-Yin *et al*. (2016). They also did not observe any correlation between UPC and SBP. From this study it can be concluded that renovascular resistance increases in diabetic dogs and it correlates significantly with glycemic status. These indices can be used as the early marker for kidney damage in diabetic patients. Among renal RI and PI, renal PI was found to be more sensitive. However, further studies are required to explore the association between the indices of renovascular resistance with disease duration and outcome in large population of diabetic dogs. So that the potential of these indices as prognostic markers can be assessed.

Conflict of interest

Authors do not have any conflict of interest.

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