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Influence of thyroid status on serum enzyme and lipid profile in dogs with chronic kidney disease

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Abstract
The present study was conducted with an attempt to evaluate the influence of euthyroidism and hypothyroidism in relation to chronic kidney disease in dogs. A total number of 72 client-owned dogs aged between two to ten years, presented to the Veterinary College Hospital, Bangalore, were included in this study. Clinically healthy dogs were assigned to Group I, euthyroid dogs with chronic kidney disease were assigned to Group II and hypothyroid dogs with chronic kidney disease were assigned to Group III. The selected dogs were in the age range of 2-4 years, >4-6 years, >6-8 years and >8-10 years with six dogs in each group. The dogs of all breeds and of either sex were included in the study. A single blood sample from the study dogs was collected at the time of presentation to clinics. Serum samples obtained were utilised for assay of aminotransferases and lipid profile using standard reagent kits. Significantly higher aminotransferase activities, total cholesterol and triglycerides were recorded in Group III compared to Group I and Group II. From the study it is concluded that the renal dysfunction exerted mild effects and hypothyroidism exerted marked influence on serum enzyme and lipid profile. Hhypothyroidism, being one of the most common causes of secondary dyslipidemia resulting in fatty liver, leading to leakage of liver specific enzymes into circulation in Group III dogs.

Keywords: Chronic kidney disease, hypothyroidism, aminotransferase, total cholesterol and triglycerides

Introduction
Maintenance of homeostasis of metabolic functions in all body organs is criticalin all living beings. Chronic kidney disease (CKD) occurs when the compensatory mechanisms of chronically diseased kidneys are no longer able to maintain adequate functions to excrete waste products, regulate electrolyte, water, and acid-base homeostasis, degrade hormones, and synthesize endocrine hormones. Thyroid hormones regulate the basal metabolic rate of all cells including hepatocytes. The liver in turn metabolizes the thyroid hormones and regulates their systemic endocrine effects [1]. The activities of aminotransferases were found to be within the normal reference rangein most of the hypothyroid dogs [2]. There are few reports of elevated aminotransferase activities in hypothyroid dogs compared to controls [3, 6]. Lower aminotransferase activities were reported in renal failure patients compared to control subjects [7, 10]. Thyroid hormones regulate the metabolism of lipids, carbohydrates, proteins and electrolytes and minerals. They mobilize the triglycerides from adipose tissue leading to increased concentration of free fatty acids in plasma. The serum total cholesterol, low LDL-cholesterol and possibly triglyceride (TG) levels increases in patients with overt hypothyroidism. Dogs with glomerular diseases and nephritic syndrome suffers with hyperlipidaemia and hypercholesterolemia [11, 12] and the prevalence of hypercholesterolemia is to the extent of 86 per cent in dogs with glomerular amyloidosis [12]. These changes could be due to increased hepatic synthesis and decreased catabolism of proteins and lipoproteins. Hypercholesterolemia and hyperlipidaemia may contribute to further renal damage. Higher concentrations of cholesterol and triglycerides is also observed in azotaemic dogs and was attributed to liver compensatory response to urinary loss of albumin associated with renal failure [13]. The present study was conducted in dogs with an objective to evaluate the influence of thyroid status and kidney dysfunction in these dogs and to study their influence on enzyme and lipid profile.

Materials and Methods

A total of 72 client-owned dogs aged between two to ten years, presented to the Veterinary College Hospital, Bangalore were included in this study. The initial screening of the dogs was done based on the case history reports and clinical signs suggestive of chronic kidney disease and those of hypothyroidism were considered. Later, the dogs were subjected to diagnostic studies which included thyroid profile, renal biomarkers profiles for final inclusion of dogs into the particular study groups. Clinically healthy dogs were assigned to Group I, euthyroid dogs with CKD were in Group II and hypothyroid dogs with CKD were in Group III. The selected dogs were in the age ranges of 2-4, >4-6, >6-8 and >8-10 years with six dogs in each age range. The dogs of various breeds and of either sex were included. Blood sample from the study dogs was collected only once at the time of presentation to clinics. Blood was processed to obtain the serum samples which were later utilized for assay of Aminotransferases (ALT and AST), total cholesterol and triglycerides using Artos-Elita® semi-automated biochemical analyser (Swemed Biomedicals Pvt. Ltd., Bangalore, India) with commercially available reagent kits supplied by M/s. Swemed Diagnostics, Bangalore. The data obtained were analysed statistically by two-way ANOVA using 'Graph Pad Prism' version 5.01 (2007).

Results and Discussion

Serum Aminotransferases

Alanine aminotransferase (ALT) is useful as a specific indicator of hepatocellular injury and is fairly liver specific in dogs and cats. ALT is at its highest activity in skeletal muscle followed by liver and cardiac muscle. AST is found in the cytoplasm and mitochondria as different isoenzymes and increases in the cytoplasmic AST isoenzyme occurs during mild injury whereas, increase in mitochondrial isoenzyme occurs during severe cellular injuries.

Significantly higher serum ALT activities in Group III compared to Group I at all stages of age (Table 1) indicates the additive effect of both hypothyroidism and chronic kidney disease in elevating the serum ALT levels in the present study.

Significantly higher serum AST activities in Group III compared to Group I and Group II at various stages of age (Table 1) indicates the primary influence of hypothyroidism in elevating the serum AST activities in that group.

With respect to hypothyroidism, the present study observations are in agreements with the findings in hypothyroid dogs [4, 6]. Similar observations were also reported in human hypothyroid subjects [14, 15]. The elevated aminotransferase activities in the present study are attributed to liver damage with evidence of metabolic changes in liver-associated laboratory parameters [14] and to cholesterol elevation due to hypo-metabolism that leads to fatty liver which might cause mild but prolonged AST and/or ALT elevation [16, 18].

With respect to chronic kidney disease in Group III, it has been reported that the level of serum aminotransferases commonly fall near the lower end of the range of the normal values in patients of CKD [8]. The pathophysiological mechanism for this reduction in the serum aminotransferase levels in patients with CKD remains controversial. The possible mechanisms include reduction in pyridoxal-5-phosphate which is a coenzyme of aminotransferase, presence of ultraviolet absorbing materials and high levels of uremic toxins. Other possibilities included decreased synthesis and inhibition of release of AST and ALT from hepatocytes or accelerated clearance from serum [8]. Lower serum aminotransferase activities could also be due to water retention and hemodilution in patients of CKD [7].

Serum Total Cholesterol

In the present study, the serum total cholesterol levels in Group III were significantly higher at various stages of age in comparison to Group I and Group II (Table 2) indicating the primary role of hypothyroidism in elevating serum cholesterol levels in Group III dogs.

Table 1: Mean ± SE values of Serum Aminotransferase (U/L) activities in different groups of dogs (n=6).

Parameter	Alanine Aminotransferase				Aspartate Aminotransferase			
Age / Group	2-4 years	>4-6 years	>6-8 years	>8-10 years	2-4 years	>4-6 years	>6-8 years	>8-10 years
Group I	31.15 ±2.31^{a}	32.5 ±12.93^{a}	36.41 ±26.05^{a}	38.83 ±2.95^{a}	19.32 ±0.77^{a}	20.69 ±1.71^{a}	21.61 ±3.57^{a}	23.77 ±1.83^{a}
Group II	39.22 ±5.36^{ab}	47.71 ± 6.16^{ab}	51.15 ±8.09^{ab}	53.03 ±6.62^{ab}	21.79 ±2.25^{a}	22.72 ±1.18^{a}	25.05 ±1.79^{a}	25.21 ±2.15^{a}
Group III	58.65 ±8.61^{b}	45.54 ± 9.18^{b}	56.79 ±8.14^{b}	86.51 ±13.39^{b}	31.12 ±2.21^{b}	35.25 ±2.77^{b}	37.70 ±3.71^{b}	38.15 ±4.21^{b}

The values with different superscripts within a column differ significantly (P<0.05).

With respect to hypothyroidism, the results are in accordance with the studies in dogs suffering from hypothyroidism [4, 19, 24] who also reported elevated serum cholesterol levels. The elevated cholesterol were attributed to decreased expression of lipoprotein receptors in the liver as demonstrated by ligand binding analysis [25]. Hypercholesterolemia in hypothyroid cases could be due to a decreased clearance and hepatic use combined with an increased hepatic production of cholesterol [19, 23]. Jiskra and coworkers attributed the elevated levels of high-density lipoproteins (HDL) in hypothyroidism to reduced activities of Cholesterol Ester Transfer protein (CETP) and hepatic lipase [30]. This results in reduced transport of cholesteryl esters from HDL-2 to very low-density lipoproteins (VLDL) and intermediate density lipoprotein (IDL) [31]. It was concluded that the hypothyroidism also leads to decreased intestinal motility that promotes increased intestinal absorption of enteric cholesterol [28].

Serum Triglycerides

In the present study, the serum triglycerides levels in Group III were significantly higher at different stages of age compared to Group I. Also, the serum triglycerides levels in Group III were significantly higher at 2-4, >4-6 and >6-8 years of age compared to Group II (Table 2) indicating the primary influence of hypothyroidism in increased triglycerides levels.

With respect to hypothyroidism, the present study observations are in agreement with the reports in hypothyroid dogs [4, 29, 31] who reported elevated triglyceride levels. The significantly higher serum triglycerides concentrations in hypothyroid dogs is attributed to poor clearance of

endogenous and exogenous triglycerides from circulation in hypothyroidism [29, 32]. Further, in patients with overt hypothyroidism, the increased serum triglyceride levels are attributed to the fact that expression of LDL receptor is modulated by thyroid hormones [33].

These results in the present study were conclusive of impaired clearance of endogenous and exogenous triglycerides from the circulation, reduced expression of LDL receptor and increased hepatic synthesis and decreased catabolism of proteins and lipoproteins due to lower levels of thyroid hormones in hypothyroidism or due to CKD as a non-thyroidal illness.

Table 2: Mean ± SE values of Serum lipids (mg/dL) in different groups of dogs (n=6).

Parameter	Total Cholesterol				Triglycerides			
Age / Group	2-4 years	>4-6 years	>6-8 years	>8-10 years	2-4 years	>4-6 years	>6-8 years	>8-10 years
Group I	189.88 ±6.45^{a}	213.17 ±9.54^{a}	224.80 ±11.74^{a}	226.23 ±9.57^{a}	121.74 ±4.76^{a}	106.24 ±10.29^{a}	120.74 ±6.29^{a}	130.70 ±8.90^{a}
Group II	200.79 ±12.76^{a}	229.94 ±20.26^{a}	238.60 ±18.74^{a}	236.47 ±18.07^{a}	121.69 ±6.51^{a}	118.72 ±6.26^{a}	125.53 ±7.86^{a}	154.56 ±4.64^{ab}
Group III	290.40 ±19.97^{b}	308.2 ± 9.35^{b}	309.32 ±10.72^{b}	309.70 ±8.80^{b}	154.55 ±6.00^{b}	152.82 ±10.89^{b}	154.39 ±6.74^{b}	172.88 ±7.39^{b}

The values with different superscripts within a column differ significantly (P<0.05).

Conclusions

Thyroid hormones through their influence on lipid metabolism could lead to hyperlipidemia during hypothyroidism which in turn might result in fatty liver causing deleterious effects on hepatocytes leading to leakage of liver specific enzymes into circulation. The results in the present study were conclusive of hypothyroidism being one of the most common causes of secondary dyslipidemia in Group III dogs which led to; (i) decreased activity of the CETP results in reduced transfer of cholesteryl esters from HDL to VLDL, thus increasing HDL-C levels, (ii) lower expression of LDL receptors in liver, results in decreased catabolism of LDL and IDL, (iii) decreased intestinal motility that might promote intestinal absorption of enteric cholesterol, (iv) decreased cholesterol utilization due to reduced metabolism and (v) increased hepatic synthesis and decreased catabolism of proteins and lipoproteins probably as a result of a liver compensatory response to the loss of proteins.

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