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# Investigation of Homocysteine Levels in Healthy Dogs

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## Abstract

Homocysteine is a parameter that plays an important role for diagnosing several diseases mainly cardiovascular diseases. In this study, the first time reference values for homocysteine levels detected in healthy Golden Retriever, Terrier, German Shepherd and Labrador Retriever breeds of dogs play an important role in the prognosis of many diseases. In this study, 10 German Shepherd, 10 Golden Retriever, 10 Labrador Retriever, and 10 Terrier breeds of healthy dogs were used. Plasma homocystein levels were measured according to commercial test kit (axis®homocyste EIA-UK) using the ELISA test kit device. Biochemical parameters were spectrophotometrically measured with the commercial test kit (Randox ®-UK) according to the specified procedures (5010 Photometer Boerringer Mannheim). In the study plasma homocysteine levels in four breeds detected as 10.60±4.55 µmol/L in the German Shepherd breed, 11.43±6.10 µmol/L in the Golden Retriever breed, 9.40±3.83 µmol/L in Labrador Retriever breed, and 8.88±2.34 µmol/L in Terrier breed. Furthermore, serum AST, ALT, LDH, albumin, urea, creatinine, TP, CK, CK-MB, and vitamin $B_{12}$ levels of the four breeds were similar to reference values reported for healthy dogs. It is for the first time, homocysteine level recorded in various breeds of healthy dogs.

**Keywords:** Dog, Homocysteine

**List of abbreviations:** Hcy: Homocysteine; CK: Creatine kinase; LDH: Lactac dehydrogenase; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; CK-MB: Cardiac origin creatine kinase; WBC: Leukocyte; RBC: red blood cell; LYM: lymphocyte; Hb: hemoglobin; Hct: hematocrit; MCV: mean corpuscular volume; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; PLT: platelet (PLT)

## Introduction

Homocysteine is a sulfur-containing amino acid which does not exist in proteins and formed from methionine during transmethylation [1-3]. Methionine is an essential amino acid produced during break down of endogenous proteins and also produced from diet proteins [1]. Homocysteine studies particularly in human medicine are determined to be associated with many diseases [1,4]. In many studies, relationship between homocysteine and many diseases like diseases of heart, kidney, liver, and thromboembolism was determined and increased level of homocysteine is important for the early diagnosis of these disorders [1,4-7]. Nowadays, cardiovascular diseases in small animals become important. Accordingly, enzymes such as Creatinine kinase (CK), lactate dehydrogenase (LDH), aspartate aminotransferase (AST), alanine aminotransferase (ALT) and creatinine kinase of cardiac origin (CK-MB) are used to evaluate cardiovascular diseases of animal and diagnosis of the diseases [8]. However, these markers can also be used in other diseases and therefore more specific search parameters are required to evaluate cardiovascular diseases. In recent years, homocysteine has emerged as a current parameter to demonstrate the cardiovascular diseases [1,2]. However, an elevated homocysteine level in various researches indicates a positive correlation between cardiovascular diseases and most cardiovascular for homocysteine have been reported to be associated with diseases [9,10]. In this study; it is aimed to identify and obtain additional reference parameters for healthy dogs and obtain additional diagnosis and prognosis references used for many diseases and cardiovascular diseases. It's a good idea to explore the analysis of homocysteine to identify early cardiovascular diseases in dogs, however the authors should bring more information about homocysteine in dogs.

## Material and Methods

### Animal material

The material in this study consisted of 40 dogs which were registered to Izmir Mavivet veterinary clinic. The dogs were regularly vaccinated according to a vaccination schedule. All dogs were found healthy on clinical examination by checking body temperature, respiratory and heart beat frequency and general clinical appearance. All dogs were divided into four groups based on their breeds (10 German Shepherd Dogs, 10 Golden Retriever dogs, 10 Labrador Retriever dogs, and 10 Terrier dogs) and each group included 10 dogs. All dogs in the study adhered to the principle of local Ethics Committee.

## Blood samples

Blood samples were taken from v. cephalica antebrachii in accordance with the technique. Blood samples were collected into EDTA containing tubes for measuring hematological and biochemical parameters from all dogs. Serum was extracted from blood samples and put into anticoagulant-free tubes and centrifuged on 3000 RPM (Rotofix 32 – Hettich). Obtained serum samples were preserved in -20 ˚C to be analyzed. Blood samples were put in anticoagulated tubes analyzed at the same day for hematologic parameters.

## Measurement of biochemical parameters

Plasma Hcy levels were determined by ELISA using commercial kit (Homocysteine AXIS, Catalog no: 802865065) as described in the procedure. Measurement of serum vitamin $B_{12}$ (Vit. $B_{12}$) was performed with autoanalyser (Elecyc 2010 Roche Hithaci-Japan) device. From the obtained serum, level of creatine kinase (CK), lactate dehydrogenase (LDH), aspartate aminotransferase (AST), alanine aminotransferase (ALT) and cardiac origin creatine kinase (CK-MB) were spectrophotometrically measured with the commercial test kit (Randox ®-UK) according to the specified procedures (5010 Photometer Boerringer Mannheim).

## Measurement of haematologic parameters

Leukocyte (WBC), red blood cell (RBC), lymphocyte (LYM), hemoglobin (Hb), hematocrit (Hct), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), and platelet (PLT) counts were measured with hemogram device (Urit 2900 Plus Vet).

## Statistical analysis

The data were analyzed using SPSS 20 for Windows. Hematological and biochemical parameters were stated as Mean, Standart Deviation values. Statistically significance level was taken as 5%.

# Results

## Haematological Findings

Haematological parameters of healthy dogs are given in Table 1 and hematological parameters on the basis of age of healthy dogs were also given in Table 2. Analysis of haematological parameters made on the basis of breed; LYM value of the Terrier Golden Retriever, Labrador Retriever and German Shepherd of dogs LYM were higher as numerical values (P<0.01, P<0.05) (Table2). Haematological parameters of healthy dogs were in physiological limit and observed to be in harmony with each other when examined on the basis of age.

| Parameter | German Shepherd (n=10) $\bar{X} + SD$ | Golden Retriever (n=10) $\bar{X} + SD$ | Labrador Retriever (n=10) $\bar{X} + SD$ | Terrier (n=10) $\bar{X} + SD$ |
|---|---|---|---|---|
| Age ( Year) | 0.90±1.29 | 1.80±1.03 | 2.60±1.51 | 2.50±1.72 |
| WBC (x10$^9$/L) | 12.17±2.20 | 13.10±3.24 | 11.81±2.91 | 12.99±4.05 |
| LYM (%) | 24.71±5.96$^a$ | 19.34±6.75$^c$ | 25.16±6.50$^a$ | 30.83±12.51$^b$ |
| RBC (x10$^{12}$/L) | 6.69±0.95 | 6.67±0.70 | 6.40±1.30 | 6.47±1.04 |
| Hb (g/dl) | 15.67±2.47 | 16.60±2.71 | 15.48±3.52 | 15.450±3.93 |
| Hct (%) | 49.56±7.80 | 49.31±7.05 | 48.93±10.09 | 47.97±7.27 |
| MCV (fL) | 74.29±5.74 | 73.53±6.06 | 76.38±5.95 | 75.76±6.81 |
| MCH (pg) | 23.44±2.42 | 25.02±4.06 | 23.99±1.97 | 23.93±2.37 |
| MCHC (g/dl) | 31.82±4.94 | 31.76±12.88 | 31.73±4.96 | 32.05±6.04 |
| PLT (x10$^9$/L) | 233.70±58.15 | 216.90±49.12 | 223.20±57.55 | 193.50±87.213 |

The difference is statistically different letters in the same line it was important. ab: P<0.01; ac: P<0.05

**Table 1:** Haematological parameters in healthy dogs

| Parameter | 1 year ( age) (n=16) $\bar{X} + SD$ | 2 years (age) (n=10) $\bar{X} + SD$ | 3-6 years (age) (n=14) $\bar{X} + SD$ |
|---|---|---|---|
| WBC (x10$^9$/L) | 13.75±3.74 | 13.87±3.10 | 11.45±2.24 |
| LYM (%) | 20.97±11.05 | 28.91±15.05 | 24.63±6.78 |
| RBC (x10$^{12}$/L) | 6.14±0.61 | 7.07±0.90 | 6.57±1.35 |
| Hb (g/dl) | 14.92±2.56 | 17.14±2.71 | 15.97±3.74 |
| Hct (%) | 45.09±5.36 | 52.31±7.16 | 49.54±9.01 |

| Parametre | 1 year ( age) (n=16) $\bar{X} + SD$ | 2 years (age) (n=10) $\bar{X} + SD$ | 3-6 years (age) (n=14) $\bar{X} + SD$ |
|---|---|---|---|
| MCV (fL) | 73.58±5.58 | 74.16±5.64 | 76.24±6.44 |
| MCH (pg) | 24.21±3.21 | 24.28±3.18 | 24.24±2.05 |
| MCHC (g/dl) | 33.31±6.55 | 33.17±6.69 | 32.16±5.22 |
| PLT (x10$^9$/L) | 208.69±73.41 | 225.00±66.31 | 212.71±74.99 |

**Table 2:** Haematological parameters on the basis of age in healthy dogs

## Biochemical findings

Biochemical parameters of healthy dogs classified according to breeds were given in Table 3. Biochemical parameters on the basis of the gender of healthy dogs were given in Table 4 and biochemical parameters on the basis of the age of healthy dogs were given in Table 5. LDH parameters in Labrador Retriever and Terrier breeds of dogs were higher than those of other races (P<0.01). Serum CK levels in Golden Retriever breed were significantly higher than those of other races (P<0.01). While Serum glucose, AST, LDH, CK, albumin, and plasma homocysteine level in male dogs were higher than female dogs. Serum urea, creatinine, ALT, CK-MB, TP and vitamin $B_{12}$ levels were lower. But these differences were not found statistically significant. All dogs were classified according to age into three groups as 1, 2, and 3-6 years. According to the statistical analysis in three group, there was no statistical significance between the biochemical parameters (P>0.05). However, the homocysteine levels in 3-6 years old group was higher than other age groups numerically, while the youngest group homocysteine levels were lowest, but they were not statistically significant (P>0.05).

| Parameter | German Shepherd (n=10) $\bar{X} \pm SD$ | Golden Retriever (n=10) $\bar{X} \pm SD$ | Labrador Retriever (n=10) $\bar{X} \pm SD$ | Terrier (n=10) $\bar{X} \pm SD$ |
|---|---|---|---|---|
| Glucose (mg/dl) | 93.90±17.07 | 94.30±12.54 | 91.60±16.91 | 91.80±23.97 |
| Urea (mg/dl) | 29.40±6.50$^a$ | 28.50±8.50$^a$ | 40.00 ±16.24$^b$ | 32.82±14.25$^a$ |
| Creatinine (mg/dl) | 0.82±0.31 | 0.76±0.24 | 0.93 ±0.20 | 0.87±0.15 |
| AST (U/L) | 28.96±6.98 | 26.00±9.85 | 27.46 ±9.69 | 23.40±6.94 |
| ALT (U/L) | 48.30±56.18 | 31.38±24.33 | 31.72±11.38 | 32.40±11.43 |
| LDH (U/L) | 67.10±31.92$^a$ | 84.50±45.95$^a$ | 110.50±63.44$^b$ | 115.50±65.91$^b$ |
| CK (U/L) | 88.50±67.41$^a$ | 148.60±105.68$^b$ | 97.60±83.36$^a$ | 110.70±92.67$^a$ |
| CK-MB (U/L) | 44.80±21.50 | 61.40±30.15 | 49.80±33.41 | 55.50±32.23 |
| TP (g/dl) | 6.51±0.81 | 5.95±0.74 | 6.08±0.25 | 6.13±0.72 |
| Albumin (g/dl) | 3.78±0.20 | 3.62±0.62 | 3.74±0.35 | 3.76±0.25 |
| Hcy (µmol/L) | 10.60±4.55 | 11.43±6.10 | 9.40±3.83 | 8.88±2.34 |
| Vit. $B_{12}$ (pgm/L) | 319.90±148.75 | 241.30±112.12 | 364.20±162.0 | 283.20±143.03 |

The difference is statistically different letters in the same line it was important. ab: P<0.01; ac: P<0.05
**Table 3:** Biochemical parameters on the basis of breed of healthy dogs

| Parameter | Male (n=20) $\bar{X} + SD$ | Female (n=20) $\bar{X} + SD$ |
|---|---|---|
| Glucose (mg/dl) | 97.41±14.57 | 87.19±17.94 |
| Urea (mg/dl) | 32.36±12.22 | 33.71±13.66 |
| Creatinine (mg/dl) | 0.82±0.20 | 0.87 ±0.26 |
| AST (U/L) | 28.22±9.41 | 24.60±7.07 |
| ALT (U/L) | 32.30±8.84 | 39.21±42.65 |
| LDH (U/L) | 105.50±52.96 | 85.10±56.48 |
| CK (U/L) | 128.32±102.97 | 87.95±76.48 |
| CK-MB (U/L) | 50.64±24.48 | 53.67±36.55 |
| TP (g/dl) | 6.03±0.50 | 6.33±0.75 |
| Albumin (g/dl) | 3.75±0.32 | 3.71±0.44 |
| Homocysteine (µmol/L) | 10.06±3.05 | 9.97±5.39 |
| Vitamin $B_{12}$ (pgm/L) | 287.09±125.35 | 341.18±174.35 |

**Table 4:** Biochemical parameters on the basis of gender in healthy dogs

| Parameter | 1 year ( age) (n=16) $\bar{X} + SD$ | 2 years (age) (n=10) $\bar{X} + SD$ | 3-6 years (age) (n=14) $\bar{X} + SD$ |
|---|---|---|---|
| Glucose (mg/dl) | 89.75±13.75 | 101.00±19.12 | 90.64±14.42 |
| Urea (mg/dl) | 31.8±9.86 | 29.30±8.73 | 33.07±11.26 |
| Creatinine (mg/dl) | 0.74±0.22 | 0.88±0.17 | 0.89±0.19 |
| AST (U/L) | 29.70±7.98 | 22.87±8.53 | 22.28±3.52 |
| ALT (U/L) | 35.78±17.72 | 27.60±11.08 | 30.17±10.44 |
| LDH (U/L) | 100.25±67.60 | 84.20±23.89 | 99.00±58.53 |
| CK (U/L) | 139.94±89.40 | 115.10±74.56 | 62.57±37.00 |
| CK-MB (U/L) | 61.31±28.26 | 43.50±20.26 | 47.00±27.17 |
| TP (g/dl) | 5.86±0.43 | 6.27±0.70 | 6.59 ±0.69 |
| Albumin (g/dl) | 3.82±0.28 | 3.56±0.41 | 3.66±0.46 |
| Hcy (µmol/L) | 9.81±3.04 | 10.05±4.89 | 11.57±4.82 |
| Vit $B_{12}$ (pgm/L) | 306.86±168.19 | 276.20±76.68 | 281.29±141.16 |

**Table 5:** Biochemical parameters on the basis of age in healthy dogs

## Discussion

History information as well as clinical, hematological and biochemical findings have an important place for diagnosis of animal diseases in veterinary medicine. In biochemical and clinical researches, knowing normal biochemical levels of the examined material will help earlier diagnosis, ethiology, progression, treatment and control of the disease as well as help to interpret the obtained results. In this study, hematological and biochemical parameters of healthy dog breeds have been evaluated according to gender and age. WBC and RBC values of German Shepherd, Golden Retriever, Labrador, and Terrier dog breeds was determined to be in harmony with the same parameters in healthy dogs of different sexes and breeds [11]. In addition, hemoglobin and hematocrit, MCV, MCH, MCHC, PLT and LYM values of the four races, on the basis of breeds, were not statistically significant between races (P>0.05) were similar to reference values reported for healthy dogs [12,13]. Glucose, urea, creatinine, AST, ALT, LDH, CK, CK-MB, TP and albumin levels of German Shepherd, Golden Retriever, Labrador Retriever Terrier breed of dog were similar. These values of the races are close to each other as a numerical value basis, was determined to show the importance statistically significant (P>0.05). These values were found to be similar to the reference values for healthy dogs [14]. Biochemical parameters between races are close to each other and this supports the data of other researchers [15]. In this study, serum glucose levels are 94.30±12.54 mg/dL in Golden Retriever dog, 91.80±23.97 mg/dL in Terrier, 93.90±17.07 mg/dL in German Shepherd Dog, and 91.60±16.91 mg/dl in Labrador Retriever. The statistical analysis conducted on the basis of gender is no different (P>0.05). Glucose levels of German Shepherd dogs were found to be similar to the values of researchers reporting serum glucose levels [14,15]. In a study, serum AST levels of healthy German Shepherds are reported as 24.00 and 31.10 IU/L, respectively [14]. In another study, serum AST levels in different breeds of dogs reported as 23-66 IU/L [16]. In this study, it was found that AST enzyme activities detected in all four breeds were within the normal ranges reported in literatures [14,16]. The same researchers reported that ALT levels are 43.40 IU/L and 21-102 IU/L in German Shepherd breeds and are 50.35 IU/L in Labrador Retriever breeds [14,16,17]. Nowadays, chest radiography, electrocardiography and echocardiography tests as are routinely used for dogs in evaluating the diagnosis and prognosis of heart disease. Despite performing these tests, the severity of heart diseases and uncertainties in response to treatment and in prognosis and treatment of individual patients is still continuing [18]. Despite the diagnosis and medical treatment of heart disease, mortalities resulting from heart disease of dogs remain at a high level. In this case, development of more specific blood-based biomarkers for diagnosis of heart diseases and its prognosis, in clinics of dogs and cats may be useful practically [1,18]. In recent years both in human medicine and in small animal medicine, specific biomarkers for diagnosis and prognosis of heart diseases are developed and widely reported to be used in this field [1]. Evaluating homocysteine is a commonly used parameter in diagnosis and prognosis of cardiovascular diseases [19]. Homocysteine concentrations are reported to increase in cardiovascular diseases in human medicine [1]. In the veterinary field, particularly in heart diseases high homocysteine levels are reported compared to its levels in healthy animals [20]. Despite all advances in explaining the etiology and pathogenesis of arteriosclerosis in human medicine, reasons of the diseases could not be explained [4].

In recent years, patients with atherosclerosis with unidentified risk factors, hyperhomocysteinemia has been demonstrated in numerous studies performed by an independent risk factor [21]. Especially in recent years, there are many studies demonstrated relationship between increased levels of homocysteine and vascular disease and thrombosis [19]. Even homocysteine plays an important role in cardiovascular diseases [1,19,22]. Along with risk factors like smoking and obesity, hyperhomocysteinaemia has been regarded as a new modifiable risk factor for atherosclerosis and vascular diseases [1,22]. Although there are many researches on homocysteine in human medicine but there are not enough researches in veterinary medicine [20,21]. Many studies performed in veterinary medicine showed connection of high Hcy with chronic renal failure in cats in which Hcy levels were higher than in

healthy cats [3]. Homocysteine levels were identified as 7.6±4.1 mmol/L in healthy cats, 10.1±10.6 mmol/L cardiomyopathy in cats, and 8.0±4.1 mmol/L in tromboembolism cats [6]. In the same study Vitamin $B_{12}$ levels were determined as 1650±700 pg/ml in healthy cats, as 939±389 pg/ml in cats with cardiomyopathy, and 866±367 pg/ml in cats with thromboembolism. Vitamin $B_{12}$ levels in healthy cats were significantly higher than in cats with cardiomyopathy and tromboembolism ($P<0.001$) [6]. In another study related with 10 dogs with heart diseases, 4 dogs with renal diseases, 6 dogs with inflammations, 7 dogs with gastrointestinal disorders, 7 dogs with trauma, 8 dogs with neoplasms; elevated Hcy were determined in these diseases compared to healthy dogs. As a result, it was reported that the homocysteine concentration is an important parameter to monitor the prognosis of cardiac patients [21].

In this study, plasma homocysteine levels of 11.43±6.10 mmol/L in Golden Retriever breed, 8.88±2.34 mmol/L in Terrier breed, 10.60±4.55 mmol/L in the German Shepherd, and 9.40±3.83 mmol/L in Labrador Retriever were detected. In conclusion, in the veterinary field, detection of normal homocysteine levels is very important in healthy dogs. In future normal homocysteine levels which have been determined in four different breeds of dogs, will contribute to the further researches on cardiovascular diseases.

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