Blood macro (Ca, K, Mg, Na, P) and micro (Al, B, Mn, Mo, Sb, Se, Sn, Tl) element status and correlations in shelter dogs

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Abstract

This study aimed at investigating the concentrations of macro (Ca, K, Mg, Na, and P), microelements (Al, B, Mn, Mo, Sb, Se, Sn, and Tl) and interaction between elements in dogs (n=125) whole blood samples that collected from clinical healthy individuals in the shelter. Depending on bioconcentration, elements are classified as macro and micro. Some are essential for biological processes but can be toxic above tolerable concentrations. In these cases, it is necessary to monitor concentrations. Also, the deficiency or excess of micro- and macroelements may diminish the effect of substances, such as other elements or drugs, or cause them to exert toxic effects. According to the results, the high to low micro- and macroelement concentrations (ng ml^{-1}) were found to be K (113255)>Ca (108257)>P (65381)>Mg (21538)>Na (4782) and Se (339.95)>Al (86.11)>Mn (32.92)>B (11.32)>Mo (8.41)>Sb (5.22)>Sn (0.50)>Tl (0.04) respectively. Statistically significant positive (Ca-Sn, Mg-Mn, Mg-Sb, Mg-Se, P-Al, P-Sb) and negative (K-Al, K-Mn, Na-Al, Na-Sb, Na-Sn) correlations were determined. The concentrations of the macroelements were within the reference range. Mn and Se concentrations were above the reference values and there is no reference value and study data on the concentrations and biological or toxic effects of B, Sb, Sn, and Tl in dogs. Concentration ranges should be identified for the early diagnosis of conditions induced by altered element concentrations and the health impacts of these changes should be thoroughly investigated.

Introduction

In mammals, elements are required for maintaining ideal health and growth via biological processes. These elements, which are found in different forms in nature, are required for various biological functions. These elements are classified as macro- or microelements depending on their concentration in the body. Microelements (trace) are present in living organisms in low concentrations. The macroelements include calcium (Ca), phosphorus (P), potassium (K), sodium (Na), chlorine (Cl), magnesium (Mg), and sulfur (S), whereas microelements (trace) include boron (B), iron (Fe), iodine (I), zinc (Zn), copper (Cu), manganese (Mn), cobalt (Co), molybdenum (Mb), selenium (Se), chromium (Cr), lithium (Li), vanadium (V), fluorine (F), silicon (Si), and nickel (Ni) (4, 29, 35, 44). These trace elements provide chemical and molecular stabilization in cell functions and control numerous vital biological processes at tolerable concentrations (32). Some trace elements, also known as potentially toxic elements (PTEs), such as Cu, Se, and Zn, are essential to maintain metabolism, but are toxic above tolerable concentrations (27). Other trace elements, such as aluminum (Al), antimony (Sb), cadmium (Cd), mercury (Hg), tin (Sn), lead (Pb), and thallium (Tl) are non-essential and not required for the metabolism of living organisms and have also toxic effects above tolerable concentrations (25, 26). The diseases and toxic effects due to possible deficiencies or accumulations of trace elements can be determined by measuring their concentrations in the blood. Monitoring of blood concentrations is necessary when clinical symptoms triggered by increased or decreased element concentrations cannot be clearly identified (23, 25, 32). Recently, there has been an increase in the number of clinical studies that examine the changes in trace element concentrations in several diseases. The varying blood concentrations and metabolic distribution of these elements have an impact on different biochemical pathways and in cases of any imbalance, this poses a risk for numerous pathological diseases (23, 32). The metabolism of trace elements is associated with the amount of dietary intake, absorption, distribution, storage, biochemical activity, and excretion. Moreover, since trace elements can interact with each other, the deficiency or excess of one element can diminish the effect of the other element or cause toxic effects. For example, high Fe concentrations can cause Cu and Zn deficiency, and high concentrations of Zn can lead to Cu deficiency. It has been shown that excessive increases in Cu concentrations result in decreased Zn and Fe concentrations (32). A similar relationship exists between Al and Ca, Mo and S, and Tl and K, where the beneficial effects of essential elements are reversed once they are exposed to non-essential elements (15, 25, 36). There are limited studies on the measurement of macro- and microelement concentrations in animals. The reference values of some elements (Al, Mo, Sb, Tl, etc.) are either not available or differ among studies (13, 37, 39). Additionally, most reference values are based on serum concentrations (9, 13, 23, 28, 40). Only based on the serum concentration measurements, the evaluation of the elements that predominantly have intracellular functions (Cu, K, Mg, Se, Zn, etc.) can be inconclusive (22). The whole blood concentrations have been used in recent studies to determine and monitor the health status and to detect short- and long-term exposure (10, 20, 31, 33). It is crucial to improve understanding of the roles of macro- and microelements in the organism and to obtain data that can be clinically associated with physiological or pathological conditions. Accordingly, the present study aimed to determine the concentrations and correlations of macro- (Ca, K, Mg, Na, and P) and microelement (Al, B, Mn, Mo, Sb, Se, Sn, and Tl) in whole blood samples collected from dogs in Thrace region of Türkiye.

Materials and Methods

In the study, blood samples were collected from 125 (female n=73, male n=52) healthy dogs (10 months–11 years) according to no recent diagnosis of any disease in the anamnesis and clinical examination of body temperature, heart rate, respiratory rate, capillary refill time, physical and neurological conditions, weight condition, vision, hearing, urinating, defecating, appetite, etc. from shelters in the Thrace region of Turkey. For elemental analyses, 10 ml blood sample of each dog was collected from *V. cephalica antebrachium* into anticoagulant tubes, following the decision of the Local Ethics Committee (2017/02).

Standard solutions were prepared using stock solutions of the ICP multi-element standard and nitric acid (HNO_3) (Merck, Germany), and calibration curves were drawn. The blood samples were digested in the microwave system (CEM MARS, USA) in a 4-step program with 10 mL HNO_3 (70%) (600 W 100% power, 15 minutes at 210°C). Ca, K, Na, and P concentrations in the solutions were determined using an inductively coupled plasma-optical emission spectrometer (ICP-OES; Spectro Analytical Instruments, Germany) (plasma power [W]: 1400, pump speed [rpm]: 30, coolant flow [L/min]: 12, auxiliary flow and nebulizer flow [L/min]: 1). Al, B, Mg, Mn, Mo, Sb, Se, Sn, and Tl were measured using inductively coupled plasma-mass spectrometer (ICP-MS; Thermo Fisher Scientific, Germany) (plasma power [W]: 1300, pump speed [rpm]: 33 rpm, coolant flow [L/min] 13, auxiliary flow and nebulizer flow [L/min]: 0.8). The method validation was performed using the parameters of the limit of detection (LOD) (ng mL^{-1}; Ca: 48.76, K: 24.04, Mg: 2.23, Na: 4.39, P: 8.16, Al: 1.41, B: 0.37, Mn: 0.17, Mo: 0.09, Sb and Sn: 0.01, Se: 0.07, Tl: 0.06), recovery (%; 74.3-133.3), correlation coefficients (r^2) (>0.99), and relative standard deviation (rsd) (<20%). Non-parametric Spearman's test was performed to test the correlation between element concentrations after the normality test. P values of <0.05 (*) and <0.01 (**) indicated statistical significance.

Results

Arithmetic and geometric mean, median, standard error, minimum, and maximum values of macro and microelements are given in Table 1. The study findings showed that the whole blood concentrations of macro- (ng mL^{-1}) and microelements were ranked as K>Ca>P>Mg>Na and Se>Al>Mn>B>Mo>Sb>Sn>Tl. Ca and Mg mean concentrations were within the reference range, while K was lower, Na and P were higher. Ca concentrations were below the reference range in 30 samples (24%) and above in 39 samples (31.2%). The K concentrations were below (99.2%) the reference range except for 1 blood sample. Mg concentrations were below the reference range in 2 samples (1.6%) and above in 22 samples (17.6%). Na concentrations were below the reference range in 1 sample (0.8%) and above in 95 samples (76%). Na concentrations were below the reference range in 1 sample (0.8%) and above in 83 samples (66.4%). Among microelements, reference

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ranges are given only for Mn, Se and the mean concentrations determined in the present study were above these. The correlations between Ca and K, Na, Sn; K and Na; Mg and Na, Mn, Sb, Se; P and Al, Sb; Al and Mn, Sn; B and Mo; Sb and Se, Sn, Tl; Sn and Tl were statistically significant positive, while between K and Al, Mn; Na and Al, Sb, Sn were significant negative (P>0.01, P>0.05) (Table 2).

Discussion and Conclusion

The varying blood concentrations of trace elements and their relationship with each other have a significant role in numerous key physiological, metabolic, and toxicological events; thus, they have gained attention in clinical practice as well as in the field of biochemistry (6, 23, 31, 32). Reference values of microelements, such as B, Co, Mb, Sn, Cr, Li, V, F, Si, and Ni, have not been specified in dogs (13, 18, 37, 39). In this respect, the results for B, Sb, Sn and Tl in the presented study, can be used for comparison in future studies.

Table 1. Macro and microelement concentrations of blood samples (ng ml^{-1}) (n=125) and reference concentrations (ng ml^{-1}) (13-15,19, 24)

	Macroelements					Microelements							
	Ca	K	Mg	Na	P	Al	B	Mn	Mo	Sb	Se	Sn	Tl
Arithmetic mean	108257	113255	21538	4782	65381	86.11	11.32	32.92	8.41	5.22	339.95	0.50	0.04
Standard error	2018.95	1604.87	259.85	37.41	992.98	4.69	1.07	0.92	0.55	0.46	8.22	0.04	0.02
Median	104300	111700	21160	4806	65600	75.47	9.53	31.81	7.87	4.06	336.30	0.42	0.03
Geometric Mean	105968	111904	21349	4763	6396	77.71	7.88	31.42	6.02	4.46	327.37	0.35	0.03
Minimum	44500	60610	13310	3211	6660	40.37	0.21	14.32	0.26	2.42	123.80	0.01	0.01
Maximum	189500	201870	31300	6064	97320	422.60	37.27	77.96	35.89	47.04	634.40	2.55	0.08
Reference Concentrations for Healthy Dogs	90000 - 117000	170867 - 209185	16000 - 24000	3266 - 4558	26000 - 62000			20			220		

Table 2. Correlations between macro and microelements.

	Macroelements					Microelements							
	Ca	**K**	**Mg**	**Na**	**P**	**Al**	**B**	**Mn**	**Mo**	**Sb**	**Se**	**Sn**	**Tl**
Ca	-												
K	0.25**	-											
Mg	-0.04	-0.09	-										
Na	0.49**	0.49**	0.17*	-									
P	0.07	0.00	-0.01	-0.10	-								
Al	0.08	-.176*	0.05	-0.27**	0.120*	-							
B	0.03	0.01	0.16	0.08	-0.01	0.06	-						
Mn	0.16	-.287**	0.30**	-0.08	0.07	0.20*	0.08	-					
Mo	0.01	0.06	0.03	0.13	0.12	0.01	0.29**	0.00	-				
Sb	-0.05	-0.08	0.21*	-0.17*	0.17*	0.16	0.04	0.12	0.06	-			
Se	0.00	0.03	0.43**	0.04	0.03	0.03	0.12	0.10	-0.16	0.19*	-		
Sn	0.21*	-0.07	0.02	-0.21*	0.15	0.47**	0.15	0.13	-0.08	0.27**	-0.02	-	
Tl	0.08	0.02	0.03	-0.01	-0.06	-0.02	0.09	0.01	-0.02	0.22**	0.04	0.19*	-

* (P<0.05), ** (P<0.01).

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Although mostly serum samples have been used for the detection of element concentrations in the studies conducted at reference ranges (9, 23, 28, 39, 40) whole blood samples are preferred to detect the concentrations of a few elements (Mo, Pb, Sb) due to their biological mechanisms that include binding to erythrocytes (15, 25, 31). It has been suggested that measuring Pb, arsenic (As), mercury (Hg), Mo, Mn, and Se concentrations in whole blood and Cu, Zn, Fe, Mg, Ca, Na, and K concentrations in serum ensures more accurate results in terms of diagnosis (31). However, the measurement of intracellular elements, such as K, Zn, Mg, Cu, and Se, only in serum may not be sufficient (22). Trace element deficiencies in the body cause growth retardation reduced immunity, increased oxidative stress, glucose intolerance, delayed wound healing, and decreased bone density. Macro elements, such as Ca, P, and Mg are the structural elements that make up the bones in the skeletal system (3, 9, 10, 35). Na and K are the major cations of the intracellular and extracellular fluids. Na^+/K^+-ATPase activity is key to the homeostasis of osmotic pressure, the maintenance of acid-base balance, enzyme activation, and carbohydrate metabolism (35). The Ca and Na concentrations found in our study were within the normal range compared to the reference values (18, 37). In a study conducted with different dog breeds, serum Ca concentrations (ppm) were 73.21–98.59, Mg concentrations were 40.87–41.85, K concentrations were 4.72–5.18, and Na concentrations were 142.70–148.89 (23). Compared to this study, the Ca and K concentrations obtained in our study were higher and the Mg and Na concentrations were lower. There is limited data on the element concentrations of blood and other tissues in dogs and their extremely low blood concentrations make them difficult to detected. In addition, the reference values are not fully specified (10). The current methods of ICP-OES and -MS were used to measure the concentrations of trace elements in blood, plasma, and serum samples. Using these methods, toxic and trace elements in the blood can be accurately and precisely identified. However, it is likely that the devices and analyses are expensive (10, 35). Nevertheless, rapid, sensitive, and accurate detection of numerous elements by using these analysis methods, which have increasingly gained importance in human medicine, allows rapid intervention to the patient, and improves the prognosis (22). It is essential that these analysis methods become widespread in the veterinary field and that they are included in the clinical routine with the reference values of the elements to be determined for each species in serum and blood samples. Our study will increase awareness on this subject and contribute to more comprehensive studies to establish reference values for macro- and microelements in the whole blood of dogs. Trace element deficiencies and the disorders caused by them have been widely investigated in humans as compared with animals. Imbalances in trace elements may neither cause clinical signs nor be a specific sign of a disease. However, these imbalances may exacerbate various chronic and infectious diseases (10). Recent studies have suggested that trace element deficiency is associated with diseases, including heart, liver, and kidney failures and cancer (10, 41). Studies in dogs with epilepsy and primary hepatitis have also reported increased Mn concentrations (19, 39). In particular, the liver plays an important role in Mn metabolism, and most of the Mn absorbed from the gastrointestinal tract is metabolized by the liver. Although Mn is an essential element, it can cause toxicity (19). In a study, determine the reference ranges (ng L^{-1}) of serum essential trace elements in healthy dogs, Se was reported in the range of 154–447 and Mn was reported in the range of 0.14–7.44 (10). In another study, serum Se concentration (ng mL^{-1}) was reported as 300.50, Mn was 3.15 in dogs and not fully explain the differences between the studies and suggested fluctuations in blood or serum Mn concentrations as a potential factor (39). In a study of seven healthy dog breeds, serum Mn concentration was measured in the range of 0.006–0.020 ppm (23). Although the cause of low Mn concentrations has not been clearly stated, it has been reported that high concentrations of Mn could be neurotoxic. In human studies, it has been suggested that the measurement of hair concentrations of Mn is more reliable than that of blood or serum samples (14, 39). In a study, the Mn value (ng g^{-1}) in the blood of dogs living in three different regions in the range of 0.02–0.05, whereas hair concentrations were 0.02–0.15 (40). Considering this information, studies are needed to detect comparative Mn concentrations in different samples (hair, blood, serum, etc.) and to determine reference ranges in dogs. The reference concentration for blood Mn in animals is 20 µg L^{-1} (9). In the present study, the mean Mn (32.98 ng mL^{-1}) values were found to be high. Increased oxidative stress in patients may lead to the development of secondary diseases, such as tissue damage and organ failure. It has been stated that the concentrations of Se, an element with antioxidant properties, may decrease during these diseases (10, 41). It has been determined that low Se concentrations increased the incidence of neoplasms and allergies, whereas Se deficiency has been observed in dogs with diarrhea (10, 30). The reference range of serum Se in dogs has been reported to be 200–300 ng mL^{-1} (10, 39). In the present study, the mean Se (340.45 ng mL^{-1}) values were high, and the lowest blood Se concentration was 123.80 ng mL^{-1}. It is concluded that this may be due to the differences in the diets of the dogs or because of some nutrients on blood Se concentrations. In a study, the researchers have determined the concentration of Se in the range of 230–250 ng mL^{-1}; however, higher values (340.45 ng mL^{-1}) were detected in our study (40).

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In healthy dogs that were fed on a balanced diet, trace element concentrations are predicted to be at normal concentrations (10, 39). Although the dogs included in our study were fed with commercial food and remains, the dietary effect could not be revealed because the dietary element concentrations and feeding duration were not known. To determine the correlation between the dietary and blood concentrations of the elements, detailed studies where dogs are fed at certain time periods (short and long-term) with diets of known elements need to be carried out. Mo is known to be essential in animals, but there is limited information on its metabolism in dogs and its reference range has not been established (15, 39). Dietary sulfur (S) accompanied by low Mo intake is associated with chronic Cu intoxication (15, 36). Although the serum Mo concentration of 8.45 ng mL^{-1} in a study by Vitale et al. (39) was like the present study (8.44 ng mL^{-1}), the serum concentration of 0.006 ppb (5.48 ng L^{-1}) found in the study by Cedeño et al. (10) was quite low.

Recent studies regarding Al are notable, and it has been recently reported that Al, which was classified as having low toxicity in previous studies, has originated from urban and industrialized areas and is toxic to mammals and accumulates in tissues (37, 43). It plays a role in the etiology of neurological, hematologic, and respiratory diseases (8). In addition, it has been stated that Al causes cellular toxicity by replacing Ca in bone tissue (25). In a study, the serum Al concentration (1581 ng mL^{-1}) in dogs was higher than the concentration reported in our study (87.27 ng mL^{-1}) (37). In other studies, Al concentrations were reported as 136.67 and 215.14 mg kg^{-1} in hair samples of healthy dogs, whereas decreased concentrations (66.00 mg kg^{-1}) were detected in dogs with mammary adenocarcinoma (66.00 mg kg^{-1}) (7, 8). In a study conducted in three different age groups, hair Al concentrations of dogs were determined at the concentration of 84.10–110.17 mg kg^{-1} (21). In other studies, hair Al concentrations in healthy dogs have been found to be 23.1 µg g^{-1} and in the range of 297.8–937.5 µg g^{-1} (11, 34). These differences in values cannot be solely explained by the fact that the samples were obtained from different tissues, either blood or hair. Al tends to accumulate in keratinous tissues, so it is recommended to use hair tissue as a bioindicator to determine Al concentrations (8). On the contrary, since the growth rates and hair shedding time periods may vary in different breeds, hair Al concentrations have also been reported to vary in the study (11).

In animals, there is insufficient data on the biological functions, interactions with each other, and blood reference concentrations of elements, such as B, Sb, Sn, and TI, and studies on element concentrations in blood, plasma, or serum samples are limited (1, 2). B, which has been known to be involved in animal metabolism (carbohydrate, mineral, energy, enzyme activities, and embryonic development) for a limited period, produces toxic effects in high amounts (38). It has been demonstrated in a human study that blood concentrations in the control group were higher (30.00 ng g^{-1}) those that of the present study (12). Sb, a non-essential element, is generally known as toxic, but the mechanism of toxicity has not yet been understood (42). It has been reported that >95% of Sb^{3+} is found in red blood cells and approximately 90% of Sb^{5+} is found in plasma (25). In a study of pregnant women, the mean blood Sb concentration was reported to be lower (1.54 µg L^{-1}) than that reported in our results (17). In cases of chronic exposures to the non-essential element Sn, bone is the target organ where accumulation occurs. It has been reported that the mean blood concentration of Sn in erythrocytes in normal subjects was higher (0.14 mg L^{-1}) than that of the present study (25). Tl, whose biological function is not fully known, causes renal and hepatic dysfunction. It has been reported that Tl and K have common receptors, and that administration of K might be a useful intervention in response to Tl intoxication (25). Similar to our study, a study conducted with pregnant women have reported Tl concentration of <0.05 µg L^{-1} (17). In addition, although not statistically significant, a positive correlation was determined between them. The correlations between Ca and K, Na, Sn were statistically significantly positive.

Although they were not significant, there was a positive correlation between Ca and P and a negative correlation between Ca and Mg. According to the results of Tatara's study (35) on silver foxes, Ca and P concentrations were positively correlated, and both elements were positively correlated with Mg and K concentrations. In the same study, it was stated that there was a positive correlation between Se and Mn. Although it was not statistically significant, there was a positive correlation between Se and Mn in our study. A positive correlation was determined between Mg and Mn in the blood of healthy people, which is consistent with our study (16). Some studies show that excess Mn in the diet can lower Mg concentrations or support that it increases convulsions by triggering Mg deficiency (24, 26). The use of Al in the diet results in reduced Ca absorption, lower Mg concentrations, and adverse effects on P (26). When looking at the relationship between Al and these minerals in the current study, we could not find any data that supports this information. In a study, it was reported that no statistical difference was found between plasma and serum concentrations for Al and the choice of matrix (whole blood, serum, plasma) for measurements is important (5). While the correlations between Al and P,

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Mn, Sn were statistically significant positive, the correlations between Al and K, Na were negative. In addition, statistically significant positive correlations (Sb-Se, -Sn, -Tl and Mo-B) and negative correlations (Na-Sb, Sn-Na, Al-K, Na) or no literature has been found to explain the relationship between these macro and microelements.

Detecting the disorders and clinical effects induced by trace elements is challenging. There is limited literature on these disorders in dogs and the determination of reference intervals. Even in recent human studies regarding trace elements, deficiency or excess states, relationships with each other, potential usage as a diagnostic marker, and detection methods have not been fully elucidated. Thus, further studies are needed to reveal the relationships between trace elements and physiology or disease in dogs and other species. Concentration ranges should be determined for the early identification of the alterations in the metabolism driven by trace elements, and associated health consequences should be extensively examined. Establishing a reference range in healthy as well as in various disease states enables us to use these elements as clinical markers and to reveal the risks associated with the disease due to their deficiency or excess. In addition, the reference sample type (whole blood, plasma, or serum), which will be used to determine the concentrations, should be selected based on differences in the mechanisms of action of the elements or it may be a more accurate approach to use whole blood to include elements involved in intracellular functions and structures. For this purpose, it would be easy to use blood samples that can be sampled by invasive and non-traumatic methods. However, there is a need for reference studies on a few elements (B, Sb, Sn and TI) whose biological functions and interactions with other elements are not fully understood. In this regard, it is recommended to monitor blood, serum, or plasma concentrations of elements that have a negative impact on health if they are deficient or above tolerable limits. In conclusion, our study has highlighted the importance of this topic and can contribute to future studies.

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Ethical Statement

Blood samples were collected following the decision of the Local Ethics Committee (numbered 2017/02).

Conflict of interest

The authors declare that they have no conflict of interest.

Author Contributions

Conceptualization and design: FAY; Methodology: FAY, MY, NA; Sampling and laboratory analysis: FAY, MY, NA, NÖ; Statistical analysis and interpretation of the data: FAY, MY; Drafting: FAY; Reviewing and editing: FAY, MY, NA, NÖ.

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