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Research Article

Investigation of Plasma Lactate Concentration in Anemic Dogs

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ABSTRACT

In many clinical situations, the importance of determining plasma lactate level is emphasised, while the effect of type and severity of anemia on plasma lactate concentration is not fully known. It aimed to evaluate the impact of anemia type and severity on plasma lactate concentrations in dogs with anemia in this study. A total of 48 dogs (36 anemic, 12 healthy) of different breeds, ages, and sexes were included in the study. Dogs with anemia were classified according to the severity and type of anemia. Hematologic evaluations included RBC, HGB, HCT, and MCV measurements. Plasma lactate concentrations were colorimetrically tested on a point-of-care analyser. Plasma lactate levels were significantly (P<0.05) higher in dogs with anemia than in healthy dogs. Plasma lactate levels were significantly (P<0.05) higher in dogs with severe anemia than in healthy dogs. Plasma lactate concentrations of dogs with regenerative anemia were significantly higher than healthy dogs, but there was no significant difference between regenerative and nonregenerative anemia groups for plasma lactate concentrations. This study concluded that the type and severity of anemia affect plasma lactate concentrations in dogs with anemia.

Keywords: *Anemia, dog, lactate.*

Anemili Köpeklerde Plazma Laktat Konsantrasyonunun İncelenmesi

ÖZET

Birçok klinik durumda, plazma laktat düzeyinin belirlenmesinin önemi vurgulanırken aneminin tipi ve şiddetinin plazma laktat konsantrasyonuna etkisi tam anlamıyla bilinmemektedir. Bu çalışmada anemili köpeklerde aneminin tipi ve şiddetinin plazma laktat konsantrasyonlarına etkisinin değerlendirilmesi amaçlandı. Farklı ırk, yaş ve her iki cinsiyetten 36 anemik, 12 sağlıklı, toplam 48 köpek çalışmaya dahil edildi. Anemili köpekler aneminin şiddetine ve tipine göre sınıflandırıldı. Hematolojik değerlendirmeler RBC, HGB, HCT ve MCV ölçümlerini kapsadı. Plazma laktat konsantrasyonları hasta başı analizörü ile kolorimetrik olarak test edildi. Anemili köpeklerde plazma laktat değerleri sağlıklı köpeklere göre önemli (P<0,05) düzeyde yüksek bulundu. Şiddetli anemili köpeklerde, plazma laktat değerleri, sağlıklı köpeklere göre önemli (P<0,05) düzeyde yüksek belirlendi. Rejeneratif anemili köpeklerin plazma laktat konsantrasyonları sağlıklı köpeklerden önemli ölçüde daha yüksekti, ancak plazma laktat konsantrasyonları açısından rejeneratif ve nonrejeneratif anemi grupları arasında anlamlı bir fark yoktu. Bu çalışmada anemili köpeklerde aneminin tipi ve şiddetinin plazma laktat konsantrasyonlarını etkilediği sonucuna varılmıştır.

Anahtar kelimeler: *Anemi, laktat, köpek*

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Introduction

Lactate is an important biomarker whose level changes at various pathological processes produced by mammals. Measurement of blood lactate level has proven to be a helpful parameter in diagnosing, monitoring, and prognosis of different clinical syndromes in humans. Its clinical use is also increasing in small animals, and some studies show its role, especially in intensive care (Pang and Boysen, 2007; Saint-Pierre et al., 2022).

Lactate is the end product of anaerobic glycolysis. Lactate production rate increases in some conditions, such as hypoxia (Hood, 2005). Erythrocytes, skeletal muscle cells, brain, skin, and renal medulla produce lactate. While the liver removes most of the lactate produced, some are eliminated by the heart and kidney (Dugdale, 2010). Lactate is transported to the liver, which is primarily essential for its metabolism. If lactate production exceeds the liver's metabolization ability, hyperlactatemia occurs (Nel et al., 2004). Studies have shown that plasma lactate is a good predictor of treatment response and prognosis In addition, serial lactate measurements have been reliable in evaluating the response to treatment (Blutinger et al., 2021; Saint-Pierre et al., 2022). Blood lactate value is measured to determine tissue perfusion and prognosis and diagnose some disease groups in feline and canine medicine (Saint-Pierre et al., 2022).

The reference value of lactate in dogs is between 0.3-2.5 mmol/L (Hughes, 2000). 2 mmol/L plasma lactate concentration has been indicated as a target measure for veterinary and human patients (Pritte, 2006). It is graded as slight (3-5 mmol/L), moderate (5-8 mmol/L), and severe increase (>8 mmol/L) in dogs. The benefit of serial lactate monitoring has been demonstrated in multiple studies in veterinary medicine. It has increased significantly in many disease processes, such as septic peritonitis, immune-mediated hemolytic anemia, babesiosis, trauma, gastric dilatation-volvulus, and intracranial disease (Di Mauro et al., 2016; Rosenstein et al. 2018; Blutinger et al., 2021).

Anemia is not a disease but a symptom of many diseases' courses and outcomes. The laboratory finding of anemia is characterised by a decrease in the erythrocyte count or hematocrit (HCT) and hemoglobin (HGB) concentration below the physiological lower limit (Furman et al., 2014). It develops due to disrupting the balance between erythrocyte production and destruction or loss. Anemia is a common and sometimes life-threatening symptom in dogs. It can be clinically determined when the degree is moderate or severe. On the other hand, mild anemia can only be revealed with laboratory findings (Tvedten, 2010).

Anemias are classified as pathophysiologically regenerative and nonregenerative anemias. Classification schemes are based on reticulocyte count, erythrocyte indices, and pathogenesis. The response of reticulocytes to chronic hemorrhage is variable, and iron deficiency develops, with indices showing microcytosis and hyperchromasia. Nonregenerative anemias are normocytic normochromic. The pathology of regenerative anemias includes internal or external bleeding and intravascular or extravascular hemolysis. Nonregenerative anemia is due to causes such as chronic diseases, chronic kidney failure, and primary bone marrow disease (Thrall, 2012).

The primary function of erythrocytes is reoxygenation (Mohanty et al., 2014). Anemias from different etiologies cause oxidative stress by various mechanisms, and the developing oxidative stress shortens the lifetime of erythrocytes and decreases their oxygen-carrying capacity (Nagababu et al., 2008; Harvey, 2010; Iuchi, 2012). Severe anemia may produce mild to moderate hyperlactatemia without hypoperfusion, especially if the anemia is initially acute. Experimental studies of euvolemic hemodilution anemia required less than 15% PCV to increase plasma lactate. When the rate of lactate production in hypoxic tissue exceeds the rate of lactate metabolism in the body, blood lactate concentration increases. Hyperlactatemia in dogs with immune hemolytic anemia (IMHA); may result from decreased oxygen delivery to tissues due to severe anemia or systemic hypoperfusion. In this case, dogs with severe anemia, tissue hypoxia, and high lactate concentration are expected to have an increased risk of multiple organ failure, followed by death (Holahan et al., 2010).

While the importance of determining the lactate level is emphasised in many clinical situations, the effect of the type and severity of anemia on plasma lactate concentration is not fully known in anemic conditions. Therefore, this study aimed to evaluate the impact of the severity and type of anemia on plasma lactate concentrations in anemic dogs.

Materials and Methods

This study was carried out with the approval of the ethics committee decision numbered 64583101/2017/080 from the Animal Experiments Local Ethics Committee of Aydın Adnan Menderes University. The animal material of this study was composed of a total of 48 dogs, including 36 anemia dogs of different breeds, ages, and genders brought to Aydın Adnan Menderes University Veterinary Faculty Animal Hospital Polyclinics. Twelve healthy dogs were brought for general control or vaccination. Dogs that did not receive any treatment protocol before were included in the study. All dogs' descriptions, medical histories, anamnesis, physical examination findings, and laboratory analysis results were recorded. All dogs were included in the study voluntarily by informing the patient owners. Blood samples were taken from vena cephalica antebrachial tubes with EDTA (2 ml) for hemogram parameters and Heparin (2 ml) for plasma lactate determination. Care was taken to ensure that the tourniquet applied during blood collection lasted 15 seconds. Patients whose tourniquet duration exceeded 15 seconds were excluded from the study. Complete blood counts of blood samples taken into tubes containing EDTA were performed with an automatic blood count device (Abacus Junior Vet 5, Diatron, Hungary) immediately after blood collection.

The dogs were examined in two main groups healthy (control) and anemia. Dogs with anemia were grouped as mild, moderate, severe, and very severe anemic patients according to the criteria reported by Tvedten (2010). Blood samples taken into heparinised tubes were centrifuged at 3500 rpm for 10 minutes immediately after blood collection. Plasma samples obtained after centrifugation were immediately tested colorimetrically in the Euro Lyser Solo (Euro Lyser, Austria) device with the lactate test kit (Euro Lyser, Austria) according to the procedure specified by the manufacturer.

The blood samples taken from the tubes with EDTA were mixed with the same amount of New Methylene Blue dye. A thin smear was prepared from the mixture after waiting for 15 minutes at room temperature. CX31 and reticulocyte percentages were found by counting at least 1000 erythrocytes and reticulocytes in these optical fields under the microscope (Olympus, Japan). According to their reticulocyte percentages, anemia dogs were classified as regenerative and nonregenerative anemia dogs (Cowgill et al., 2003).

The arithmetic means standard error and minimal-maximal values of the parameters at the sampling time were calculated in the groups. The distribution of numerical data was evaluated using the Shapiro-Wilk test. For parameters with

normal distribution, normal distribution after transformation (logarithmic or square root), and homogeneous variance, one-way analysis of variance (ANOVA) was used in a comparison of more than two groups, differences between groups using the Tukey test in post-hoc comparison and from which group or groups the determined difference originated were tested. The Kruskal-Wallis test and posthoc comparisons were performed using the paired method for the parameters (MCV) determined not to show the parametric test assumptions. In comparing two independent groups, the Mann-Whitney U Test was used for the parameters that did not show the t-Test for the independent groups (MCV) for the normally distributed and homogeneous groups. Probability (P-value) P<0.05 was considered significant in all analyses. SPSS 22.0 (Statistical Package for the Social Sciences, IBM SPSS Statistics, Chicago, IL, USA) program was used for statistical evaluations.

Results

Statistical evaluations of red blood cell (RBC), HGB, HCT, and mean corpuscular volume (MCV) values in healthy and anemic dogs are presented in Table 1. RBC, HGB, HCT, and MCV values in dogs with anemia (n=36) were significantly lower (P<0.001) compared to healthy dogs (n=12). These hemogram parameters (HCT, RBC, HGB, MCV) and statistical results of dogs with anemia grouped according to severity are shown in Table 2. Since no dog could be found with a hematocrit value below 13%, a very severe anemia group was not formed. There were significant (P<0.001) differences in HCT value, RBC count, and HGB concentrations between mild, moderate, and severe groups in dogs according to the severity of anemia. It was determined that as the degree of anemia increased in dogs with mild, moderate, and severe anemia, the levels of HCT, RBC, and HGB decreased significantly. There was no significant difference between the mild and moderate anemia groups regarding MCV value. The MCV value was significantly lower (P<0.01) in dogs with severe anemia compared to healthy dogs.

Some hemogram parameters (HCT, RBC, HGB, MCV) and statistical results of dogs grouped according to the type of anemia are shown in Table 3. There was no significant difference between regenerative (n=20) and nonregenerative (n=16) anemia groups for HCT value, RBC count, and HGB concentrations. HCT, RBC, HGB and MCV values of regenerative and nonregenerative anemic dogs were significantly lower than those of healthy dogs.

Plasma lactate values and statistical results of healthy and anemic dogs, regardless of severity and type, are shown in Table 4. Plasma lactate concentrations in dogs with anemia were significantly higher (P<0.05) compared to healthy dogs.

Table 1. Some hematological findings (Mean±Standard Deviation, Minimum-Maximum) of healthy and anemic dogs.

Parameter	Healthy (n=12)	Anemic (n=36)	P
RBC	6.83±0.13 (6.22-7.86)	4.34±0.16 (2.32-5.82)	0.0001
HGB	13.92±0.43 (11.10-17.00)	8.38±0.34 (4.20-12.20)	0.0001
HCT	44.50±1.03 (38.48-51.24)	26.49±1.06 (14.36-36.63)	0.0001
MCV	65.08±0.74 (60.00-69.00)	61.08±0.84 (47.00-80.00)	0.001

Table 2. Some hemogram parameters (Mean±Standard deviation, Minimum-Maximum) of healthy dogs and anemic dogs grouped according to the severity of anemia.

Parameter		Severity of anemia (n=36)			
	Healthy (n=12)	Mild (n=12)	Moderate (n=12)	Severe (n=12)	P
RBC	6.83±0.13^{a} (6.22-7.86)	5.36±0.10^{b} (4.53-5.82)	4.46±0.14^{c} (3.85-5.20)	3.21±0.14^{d} (2.32-4.01)	0.0001
HGB	13.92±0.43^{a} (11.10-17.00)	10.33±0.39^{b} (8.40-12.20)	8.66±0.23^{c} (7.50-10.10)	6.16±0.30^{d} (4.20-8.20)	0.0001
HCT	44.50±1.03^{a} (38.48-51.24)	33.33±0.65^{b} (30.43-36.63)	27.20±0.69^{c} (24.19-32.16)	18.95±0.63^{d} (14.36-24.20)	0.0001
MCV	65.08±0.74^{a} (60.00-69.00)	62.25±1.11^{ab} (56.00-69.00)	61.16±0.78^{ab} (57.00-65.00)	59.83±2.15^{b} (47.00-80.00)	0.002

a, b, c, d: The difference between groups containing different letters on the same line is significant.

Table 3. Some hemogram parameters (Mean±Standard deviation, Minimum-Maximum) of healthy dogs and anemic dogs grouped according to the type of anemia.

Parameter	Healthy (n=12)	Type of Anemia (n=36)		P
		Regenerative (n= 20)	Nonregenerative (n=16)	
RBC	6.83±0.13[a] (6.22-7.86)	4.16±0.23[b] (2.32-5.68)	4.56±0.22[b] (2.47-5.82)	0.0001
HGB	13.92±0.43[a] (11.10-17.00)	8.15±0.46[b] (5.20-12.20)	8.68±0.50[b] (4.20-12.10)	0.0001
HCT	44.50±1.03[a] (38.48-51.24)	25.70±1.50[b] (17.50-36.63)	27.48±1.49[b] (14.36-35.40)	0.0001
MCV	65.08±0.74[a] (60.00-69.00)	61.90±1.23[b] (55.00-80.00)	60.06±1.08[b] (47.00-65.00)	0.003

a, b: The difference between groups containing different letters on the same line is significant.

Table 4. Plasma lactate concentrations (Mean±Standard deviation, Minimum-Maximum) of healthy and anemic dogs.

Parameter	Healthy (n=12)	Anemic (n=36)	P
Lactate	2.80±0.15 (2.18-4.10)	3.83±0.20 (0-99-7.07)	0.023

Table 5. Plasma lactate concentrations (Mean±Standard deviation, Minimum-Maximum) of healthy dogs and anemic dogs grouped according to the severity of anemia

Parameter	Healthy (n=12)	Severity of Anemia (n=36)			P
		Mild (n=12)	Moderate (n=12)	Severe (n=12)	
Lactate	2.80±0.15[b] (2.18-4.10)	4.01±0.30[ab] (2.81-6.18)	3.37±0.47[ab] (0.99-7.07)	4.10±0.25[a] (2.54-5.51)	0.021

a, b: The difference between groups containing different letters on the same line is significant.

Table 6. Plasma lactate concentrations (Mean±Standart deviation, Minimum-Maximum) of healthy dogs and anemic dogs grouped according to the type of anemia.

Parameter	Healthy (n=12)	Type of Anemia (n=36)		P
		Regenerative (n=20)	Nonregenerative (n=16)	
Lactate	2.80±0.15[b] (2.18-4.10)	3.88±0.26[a] (1.78-6.18)	3.76±0.34[ab] (0.99-7.07)	0.032

a, b: The difference between groups containing different letters on the same line is significant.

Statistical values of plasma lactate concentrations of dogs with anemia grouped according to severity are given in Table 5. According to the severity of anemia, there were no significant differences in plasma lactate concentrations between mild, moderate, and severe groups in dogs. In dogs with severe anemia, the plasma lactate value was significantly higher ($P<0.05$) than in healthy dogs.

Statistical results of plasma lactate concentrations of dogs grouped according to the type of anemia are given in Table 6. The plasma lactate concentrations of the dogs grouped as regenerative anemia according to the type of anemia were significantly ($P<0.05$) higher than the healthy dogs. Plasma lactate concentrations were not significantly different between the regenerative (n=20) and nonregenerative (n=16) anemia groups.

Discussion

Lactate measurement has become common in veterinary medicine due to its clinical utility and the increasing number of lactate analysers (Mackenzie et al., 2010). It has been reported that when the lactate production rate in hypoxic tissue exceeds the lactate metabolism rate in the body, blood lactate concentration increases (Holahan et al., 2010). While the importance of determining the lactate level in many disease states and symptoms is emphasised, the effect of the type and severity of anemia on plasma lactate concentration in anemic patients is not fully known. According to our knowledge, this is the first study to evaluate the severity and type of anemia effect on plasma lactate concentrations in anemic dogs.

Lactate concentrations can be measured from whole blood, plasma, or serum (Rosenstain et al., 2018). The term plasma lactate only refers to the lactate concentration in the plasma fraction. In contrast, whole blood lactate refers to the mean concentration of intraerythrocytic and plasma lactate fractions following red blood cell lysis (Hughes et al., 1999). It is reported that whether the blood sample taken from the patient is venous, arterial, or capillary affects the lactate value (Gallagher et al., 1997). The difference in lactate level between arterial and venous blood was determined as 0.18-0.22 mmol/L. It is reported that there is a high correlation (mean difference, 0.08 mmol/L) between venous and arterial blood lactate measurements. (Middleton et al., 2006). Researchers reported that lactate levels in venous and arterial blood samples were similar and acceptable. Gillespie et al. (2017) report that venous blood may be preferred because it is easier and less painful. Venous blood samples from dogs were selected for this study.

For accurate plasma lactate measurement, it is necessary to minimise the short vessel occlusion and the struggle for restraint (Gillespie et al., 2017). The effort affects plasma lactate concentrations, possibly depending on muscle activity (Rosenstain et al., 2018). Various studies have shown that struggle affects plasma lactate levels in healthy cats (Rand et al., 2002). It has been reported that the plasma lactate level increased rapidly and significantly in cats that applied a spray bath for 5 minutes before blood collection (Rand et al., 2002). In a smaller study of 21 cats, lactate levels of only 3 cats were found to be higher than 2.5 mmol/L (Redavid et al., 2012). A study on humans reported that blood draws by applying a tourniquet for a long time significantly increased the plasma lactate level, but temporary tourniquet applications for routine vein puncture did not significantly (Dede, 2016; Gillespie et al., 2017).

Anemia, a result of hematological and non-hematological diseases, is a crucial symptom. The most common causes are blood loss, decreased erythrocyte production, or increased erythrocyte consumption (Vuckovic and Allegreti 2015; Ray & Hemphill, 2016). The rate of lactate production increases in hypoxia (Hood, 2005). Common causes of tissue hypoxia resulting from oxygen supply/demand imbalance include hypovolemia, cardiogenic and septic shock, anemia, hypoxemia, and hypermetabolism (Torata and Raper, 1997; Zipes et al., 2005). The primary way of energy production in tissues is aerobic metabolism using oxygen. However, there is no oxygen storage system in the tissues, and convective and diffuse mechanisms provide oxygen delivery to the cells. By carrying oxygen, blood contributes to convection, that is, to delivering oxygen to cells (Leach and Treacher, 1998). The amount of oxygen reaching all cells in the body is called "oxygen delivery (DO_2)". The oxygen consumed in mitochondria is known as "oxygen consumption (VO_2)". Oxygen delivery is the partial pressure of oxygen in the blood reaching the cell. If it continues, consumption is also affected after a point called the "point where oxygen consumption becomes delivery dependent" or "critical DO_2". This is where tissue oxygenation begins to deteriorate (Rolland, 2011). An experimental model showed that the persistence of the critical level of DO_2 in the absence of treatment resulted in death within a maximum of 3 hours (Fontana et al., 1995). When the decrease in oxygen supply to the tissues exceeds a critical level, the oxidative mechanism in the cells is interrupted, and anaerobic metabolism begins.

The cardiac rate, the haemoglobin level in the blood, and the degree of saturation of hemoglobin with oxygen (SaO_2) determine the oxygen reaching the cell. A reduction in any of these is the cause of hypoxia (Zander, 1990). The decrease in hemoglobin can be called "anemic hypoxia" (Meier et al., 2012). Meier et al. (2004) reported in an experimental study that in subjects with hemodilution, and hemodynamic decompensation, an increase in lactate and catecholamine levels was observed when the critical hemoglobin level was reached and that the subjects died within 3 hours in the absence of blood transfusion. Cain (1977) reported that hyperlactatemia occurs with a decrease in HCT in dogs. In our study, plasma lactate value was significantly higher ($P<0.05$) in all dogs with anemia compared to healthy dogs. This situation is related to hypoxemia due to low oxygen transport capacity in patients with anemia.

The symptoms of anemia depend on the severity and cause of the anemia, the rate of occurrence, and the patient's age. Symptoms are usually due to hypovolemia and decreased oxygen delivery to tissues in acute anemia, such as bleeding. Signs and symptoms are more severe in considerable blood loss and acute hemolysis cases. The emergence of symptoms may be delayed until the hemoglobin concentration falls below 5 g/dl with the activation of compensatory mechanisms in chronically developing anemia. It has been shown that when the hematocrit value decreases, there is an increase in the lactate level (Fink, 2002; Dixon et al., 2003; Von Heymann et al., 2006; Huybregts et al., 2009; Garcia-Alvarez et al., 2014). However, Dixon et al. (2003) reported no correlation between increased lactate levels and hematocrit values in the intraoperative and postoperative periods. There were no significant differences in plasma lactate concentrations between mild and moderate groups in anemic dogs compared to healthy dogs in this study. However, in dogs with severe anemia, plasma lactate levels were significantly higher ($P<0.05$) than in healthy dogs. This is related to the low oxygen-carrying capacity due to anemia. However, since a very severe anemia group could not be formed, the effect of anemia at values below the critical level on plasma lactate levels could not be thoroughly evaluated.

The correlation between anemia and hyperlactatemia is highly dependent on the chronicity of the disease (Holahan et al, 2010). Clinically significant hyperlactatemia may develop in animals that become acutely anemic with secondary hemorrhage or hemolysis. In contrast, animals with chronic, severe anemia may have plasma lactate concentrations in the reference range (Holahan et al., 2010). In one study, hyperlactatemia did not develop in dogs with dilutional anemia until the hematocrit fell below 15% (Cain, 1965). Hyperlactatemia due to hypoxemia is rare in veterinary medicine, as PaO_2 values must be 25–40

mmHg before lactate concentrations start to increase (Cain, 1965; Cilley et al., 1991; Rosenstain et al., 2018). Different tissues have different tolerance to anemia. Blood flow changes because of the tissues' oxygen requirements and blood redistribution (Van Woerkens, 1992; Fan et al., 1980). Lauscher et al. (2013) reported that the determination of global oxygen supply and consumption is insufficient to determine each tissue's anemia tolerance. For example, kidney and skeletal muscle tissue show tissue hypoxia when hemoglobin is 6-7 g/dl. In this study, the plasma lactate concentrations of dogs with regenerative anemia were significantly ($P<0.05$) higher than those of healthy dogs. However, there was no significant difference between the groups with regenerative and nonregenerative anemia. As Du Pont Thibodeau et al. (2014) stated that the critical hemoglobin concentration, the point at which tissue oxygenation begins to deteriorate, and the oxygen usage conditions may be related to the variation according to the tissue and the individual.

Conclusion

While there is still much to learn about lactate measurement, it is an inexpensive and easy-to-do test that provides quick results to assist veterinarians in diagnosing and managing critically ill patients. Anemia in dogs is a life-threatening symptom, when severe, occurring as a course or consequence of many diseases. Effective and rational treatment of this symptom is possible by identifying and eliminating the disease or condition that causes anemia. The presence of concomitant tissue hypoxia in the presence of anemia is of vital importance in terms of early resuscitation and prognosis of patients. According to the results obtained from this study, it was determined that the plasma lactate level in dogs with anemia was significantly higher than in healthy dogs. In addition, it has been revealed that the type and severity of anemia may play a role in plasma lactate levels. In addition, it is thought that the data obtained can be used as a reference for wider and more comprehensive studies on dogs.

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Conflict of interest

The authors declare that they have no conflict of interest.

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