**Letter to the Editor**

Dear Drs Hinchliff and DiBartola

During our hospital’s latest internal medicine rounds, we reviewed the paper: “*Relationship between lean body mass and serum renal biomarkers in healthy dogs*” by Hall JA et al.1 The study examines the effects of lean body mass on renal biomarkers in dogs, and aims to provide further validation for the use of symmetric dimethylarginine (SDMA) as a marker of glomerular filtration rate (GFR) in dogs. Most clinicians would agree that SDMA is an exciting new biomarker that has the potential to improve diagnosis and management of chronic kidney disease (CKD) patients. As a result, we enjoyed reviewing the paper, and it certainly stimulated discussion amongst colleagues. Since this work was a retrospective analysis of samples collected from a previous study,2 we were also prompted to read the original paper concurrently.

Of particular interest was the observation of a ‘time on diet effect’ for SDMA concentrations, which decreased significantly in dogs of all treatment groups. The authors suggested that this effect might be due to improved in GFR in the study dogs, but we wondered whether there might be an alternative explanation? Therefore, we wish to make some observations on both papers, which we hope will be of value to readers of *Journal of Veterinary Internal Medicine*, and would very much welcome the thoughts of the authors on these matters. For the sake of clarity, we will use the term “original study” for the *PLOS ONE* paper,2 and “SDMA study” for the *Journal of Veterinary Internal Medicine* paper.1

The original study was a 6-month feeding trial comparing three diets: a control diet and two ‘test diets’, comprising the control diet with added L-carnitine and/or fatty acids. All dogs were healthy, without evidence of chronic kidney disease (CKD), and the control diet was a commercially available phosphorus-restricted ‘therapeutic diet’ designed for feeding to dogs with CKD. However, before the start of the study, dogs were fed a ‘pre-trial’ food, which was a standard complete and balanced adult canine food. Nutrient contents of all diets are reported in the original study, and reveal marked differences between the pre-trial food and the control/test foods for protein (18% vs. 14% as fed [AF]), fat (8% vs. 18% AF), and phosphorus (0.7% vs. 0.3% AF) content.2 Given these differences, is it possible that the ‘time on diet effect’ might be related to the switch from the pre-trial to the test/control diets? It is noteworthy that a ‘time on diet effect’ on SDMA concentrations was not observed in a similarly-designed study in colony cats.3 However, a key difference between the original study and this feline work was the fact that cats were fed the phosphorus- and protein-restricted diet *both before and during* the study.

Second, in both the original study and the SDMA study, the authors state: “*fresh food was offered daily with amounts calculated to maintain body weight*”.1,2 However, in the original study, body weight increased significantly in all groups (by an average of 6-8%, depending upon the diet group).2 Lean tissue mass was unchanged, but fat mass increased by an average of 15-30%, depending upon the diet group. This is a substantial increase in body fat for a 6-month period and implies that the dogs were actually in a state of positive energy balance, rather being fed at maintenance energy requirements.

Third, in the original study, serum BUN, creatinine, phosphorus were measured.2 Whilst serum creatinine was unchanged during the study (which is similar to the results reported in the SDMA paper), BUN decreased significantly, perhaps reflecting the difference in dietary protein intake between the pre-trial and study diets. However, a significant increase in phosphorus concentrations was also observed in all diet groups during the study.1 Whilst this may not have been of clinical significance (since phosphorus concentrations remained within the reference interval throughout), the finding would not be consistent with an improvement in GFR, which is the suggested mechanism for the decreased SDMA concentrations over time in the SDMA paper.1 Did the authors measure GFR using another method, such as iohexol clearance, to confirm their theory?

In light of these observations, we wondered whether the authors would be willing to report the SDMA results for each group at every time point (0 months, 1 month, 3 months and 6 months), so as to illustrate the change in SDMA concentrations over time more clearly? Although there may be various explanations for the ‘time on diet effect’ on SDMA concentrations (e.g. GFR alterations, a possible diet effect, an effect of positive energy balance, or due to gain in fat mass), it is arguably most critical to clarify whether a diet effect might exist for standard maintenance diets versus phosphorus-restricted diets. Therefore, we would very much value the authors’ insight into this possibility, for instance whether there are data from other studies in dogs that have assessed the influence of diets with differing nutrient content on serum SDMA concentrations.

The International Renal Interest Society (IRIS) provides guidelines for managing dogs with CKD, and gives recommendations on treatments to consider at different stages.4 It is currently recommended that dietary modification (with a phosphorus-restricted diet) be considered when serum phosphorus concentration exceeds certain cut points (e.g. 4.6 mg/dL for IRIS stage 2). Thus, it is common to change from a standard canine maintenance diet to a therapeutic renal diet during the course of management. Further, appetite can be highly variable in some patients, and this can necessitate either switching amongst the phosphorus-restricted therapeutic diets, or adding other food to improve palatability and compliance. Therefore, before the use of serum SDMA can be recommended for monitoring patients with CKD, it is vital for clinicians to have reassurance that this marker is not affected by factors other than GFR, and especially diet.

Finally, we wish to disclose our own potential conflicts of interest. None of the authors has a financial association with any commercial company offering clinicopathological testing in veterinary species. However, Royal Canin financially supports the academic post of one of the authors (German), and the same author is also in receipt of research funding from this sponsor. Nonetheless, the studies in question have not been discussed with the sponsor prior to writing this letter, and the sponsor was neither responsible for the decision to write this letter, nor aware of any of its contents prior to submission.

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**References**

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