Letter to the Editor

The Contribution of Nutrition to the Protective Value of High Plasma Aldosterone Concentrations in Hemodialysis Patients

To the Editor:

I would like to congratulate Dr. Kohagura and his colleagues for their work on the prognostic value of plasma aldosterone concentrations (PAC) in patients on hemodialysis (*1*). Their work contributes significant insight into this subject. Many years ago, we evaluated the significance of PAC upon nonrenal potassium elimination in diabetic patients on dialysis. In that study, we found a group of patients who were unable to mount an aldosterone response to hyperkalemia and who maintained persistently low levels of aldosterone despite a potassium challenge (*2*). More recently, when the clinical significance of aldosterone expanded beyond that of a mineralocorticoid hormone to include nonclassical actions of vascular remodeling and cardiac function irrespective of potassium supplementation (*3*), we returned to that data and evaluated the effect of the levels of aldosterone on survival in hemodialysis patients. As Kohagura notes, since aldosterone blockade is thought to promote improved survival, we had expected that those patients who were unable to mount an aldosterone response would be more likely to have a favorable survival. All of the patients in our original study were deceased by that time. Similar to Kohagura we found that the inability to secrete aldosterone appeared not to be protective, and instead an improved survival was found in those patients with higher aldosterone level (Fig. 1) (*4*).

One critic of our work at that time felt that "any simplistic correlation of serum aldosterone levels with target organ dysfunction is overly simplistic" (*5*). That critic felt that since synthesis of aldosterone occurs at extra-adrenal sites, including the endothelium and vascular smooth muscle cells (VSMC), vascular cells *per se* are aldosteronogenic, and thus it is the locally produced aldosterone in the vascular endothelial cells that may act on the VSMC in a paracrine manner (*6*), while the circulating levels are likely to be irrelevant. Secondly, the dissociation of mortality from PAC is consistent with the formulation that the determinants of aldosterone effects include both ambient aldosterone levels and aldosterone responsiveness *per se*. Observations in hypertensive rats by Horiuchi *et al*. (*7*) and Takeda *et al*. (*8*) are consistent with an increase in aldosterone responsiveness. Consequently, only utilization of aldosterone receptor antagonists as a pharmacological probe can rigorously unmask the pathogenetic role of aldosterone (*5*). Yet the data of Kohagura do not appear to be random or unrelated but indeed seem to indicate that higher circulating PAC in hemodialysis patients are again associated with improved chances of survival.

The other criticism of our work is also answered by Kohagura's data. It was felt that since we had not controlled the volume during the interdialytic intervals, one could not assess the role of volume on aldosterone (*5*), and "therefore any determinations of aldosterone in ESRD patients without rigorous maintenance of the constancy of volume during the interdialytic period usually confounds the observed results" (*5*) (ESRD: end-stage renal disease). At that time we felt that the criticism was invalid, since hyperkalemia is a stronger stimulus for aldosterone secretion than volume, but now the data of Kohogura provide more insight into this phenomenon. First, Kohagura has found that the PAC remains fairly constant with subsequent annual follow-up, demonstrating that our measurements were reliable and not as variable as was predicted by our critics. Secondly, as seen in the data of Kohagura, the interdialytic weight gains of his higher PAC group were statistically greater ($p<0.001$), yet the higher weight gains should have had a deleterious effect upon mortality (*9*), rather than a protective one as was found.

Any reason for the protective effect of higher PAC levels in hemodialysis remains purely speculative at this point. Like Kohogura, we did not find sodium and volume loading to be risk factors; however, unlike Kohogura, we do not feel that potassium played a role since all of our patients were hyperkalemic, but only those who were able to mount a high aldosterone response to the high potassium levels demonstrated improved survival. Furthermore, it has been previously shown that potassium supplementation does not affect the deleterious effect of aldosterone (*3*). When our data was fur-

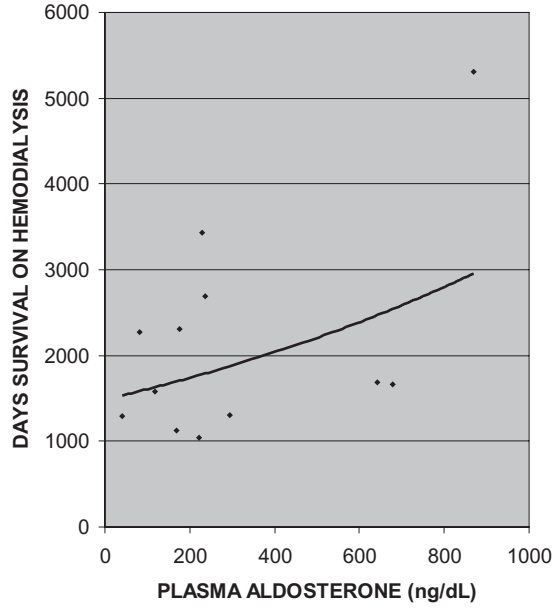

Fig. 1. *Effect of plasma aldosterone concentration on survival of hemodialysis patients.*

ther reviewed, it was felt that perhaps better nutrition was responsible for the higher potassium levels and the greater survival (*10*). Similarly, since the higher weight gains of Koagura's high PAC group would have been more likely to be associated with better nutritional indices (*11*), and since the significance of the lower PAC found by Kohagura became marginal by the addition of albumin, one would think that nutrition may be the most important factor in this phenomenon. Indeed, it may be improved nutrition, which results in both hyperkalemia and higher PAC, that is responsible for the improved survival.

While the role of aldosterone in endothelial dysfunction is clear and its deleterious effect on survival of patients with cardiovascular disease is undisputed, the effect of PAC in patients with end-stage renal disease may not be what many have predicted. Often risk factors for overall and cardiovascular mortality in the general population, such as a high cholesterol (*12*), obesity (*13*, *14*) or hypertension (*13*, *14)*, are either not found to be risk factors or are paradoxically associated with improved survival. Such may be the case with circulating plasma aldosterone levels, although this may not necessarily preclude the benefits of local aldosterone blockade.

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Response to: The Contribution of Nutrition to the Protective Value of High Plasma Aldosterone Concentrations in Hemodialysis Patients

To the Editor:

We thank Dr. Diskin for his interest in our article (*1*) and for providing his original data, which support our observation. In agreement with our data, Diskin and colleagues also showed that a lower rather than higher plasma aldosterone concentration (PAC) after a potassium challenge is associated with poor survival among hemodialysis (HD) patients (*2*).

Additionally, Diskin's data show that a low PAC might not change even after a potassium challenge. We had thought that the lower PAC value might be due to an absence or scarcity of stimulators of aldosterone (Ald) secretion, such as renin and potassium; however, Diskin's data showed that the lower PAC was due in part to a decrease in the potential to secrete Ald under such conditions as the potassium challenge.

Diskin has also reported that the patients who are unable to mount an Ald response to such high potassium levels are usually those with hyporeninemic hypoaldosteronism, and are thus more likely to have end-stage renal disease due to diabetes (*2*). He also showed that hypo-responsiveness of Ald secretion is associated with poor survival. The fact that a significant proportion of Diskin's patients with hypo-responsiveness of Ald secretion had diabetes might be partly responsible for the poor survival rate in his study. In our study, non-diabetic patients with lower PAC also had a poorer survival rate than those with higher PAC. Therefore, the lower PAC itself or related factors might be associated with the poorer survival. We believe that, as Diskin noted, malnutrition may be partly responsible for the association between poor survival and lower PAC, since albumin levels in the lower PAC group were lower than those in the higher PAC group. However, we found no differences in other markers of nutrition, such as body mass index or total cholesterol level, between the two groups. Among the patients with lower PAC, the lower potassium subgroup had a poorer survival rate than the higher potassium subgroup. Most subject deaths in the lower potassium/lower PAC (LkL) subgroup were due to infection, while there was only one death due to infection in the higher potassium/lower PAC (HkL) subgroup. Interdia-

Table 1. Comparison of the Characteristics of the Low Potassium/Low Plasma Aldosterone Concentration and High Potassium/Low Plasma Aldosterone Concentration Subgroups of Non-Diabetic Patients

Variable	Lower K/Lower PAC (n=25)	Higher K/ Lower PAC (n=24)	p value
Age (years)	65.7±15.0	61.3/11.7	n.s.
BMI (kg/m^2)	21.8±3.3	21.3±2.5	n.s.
% BW reduction	3.4±1.8	4.5±1.4	0.004
CTR (%)	52.0±4.5	53.4±4.5	n.s.
Albumin (g/dL)	3.9±0.4	3.9±0.3	n.s.
K-pre HD (mEq/L)	4.6±0.6	5.8±0.4	<0.001
K-post HD (mEq/L)	3.5±0.4	3.9±0.4	<0.001
PRA (ng/mL/h)	2.0±3.1	1.2±1.1	n.s.
PAC (ng/dL)	10.4±7.5	13.6±8.9	n.s.
PAC/PRA ratio	10.5±8.3	20.9±18.6	0.019
Cause of death			
CVD/Non-CVD (infection)	1/8 (6)	3/3 (1)	0.03

Data are expressed as means±SD. K, potassium; PAC, plasma aldosterone concentration; BMI, body mass index calculated with predialysis body weight; % BW reduction, % body weight reduction per session; CTR, cardiothoracic ratio; HD, hemodialysis; PRA, plasma renin activity; CVD, cardiovascular disease. Low PAC: <29.6 ng/dL; high PAC: ≥29.6 ng/dL; low K: <5.3 mEq/L; high K: ≥5.3 mEq/L. The unpaired t-test and the χ^2 test were used to analyze differences in discrete variables between the groups.

lytic body weight gain was significantly lower in the LkL subgroup compared with the HkL subgroup, while measured albumin levels of the subgroups were quite similar. Taking into account the dilutional effect on albumin level, the actual albumin level at dry weight might be lower in the LkL subgroup. These findings indicate that the LkL subgroup might include many malnourished patients, and indeed, we have commonly encountered malnourished patients complicated with infections. Impaired potassium current in T-lymphocytes has been shown to be one of the factors responsible for the decreased immune response during malnutrition (*3*). We would like to focus on our observation that a higher level of Ald has little effect on fatal cardiovascular disease (CVD) in HD patients. In our study, only 1 patient died due to CVD among 64 higher PAC patients (*1*). Diskin points out that improved nutrition might contribute to the excellent survival in patients with higher PAC; we believe that a balance between PAC and sodium might be another successful mechanism. It is well known that Ald *per se* cannot exert an adverse effect on the cardiovascular system. Most previous studies showing adverse effects of Ald on the cardiovascular system were carried out under conditions such as sodium loading or volume excess (*4*–*6*). However, the adverse effects of Ald have been reported to be minimal without sodium loading even at relatively higher PAC levels (*7*). Patients receiving maintenance HD are prone to have such conditions as sodium and water excess. This led us to ask, did our subjects with higher PAC suffer from these conditions? To examine this question, we focused on a marker of volume status in each group. In the higher PAC group, the cardiothoracic ratio (CTR) was relatively smaller, although the interdialytic body weight gain was significantly higher than that of the lower PAC group. These findings indicate that the average volume status over a week might be lower in the higher PAC group than in the lower PAC group. The adverse effect of Ald might not be observed even under higher PAC conditions due to the lower average volume status.

It remains to be determined whether there is any pathogenic role of Ald among patients with lower PAC, who are assumed to be under volume excess. Subgroup analysis might help in resolving this issue. Among non-diabetic patients with lower PAC, the HkL subgroup showed a higher survival rate than the LkL subgroup. However, 50% of deaths in the HkL subgroup were due to CVD. In the LkL subgroup, in contrast, only 11% of deaths were due to CVD, and most of the other deaths were associated with infection (6 of 8 non-CV deaths) (Table 1). Compared with the LkL subgroup, the HkL subgroup might be under pronounced volume excess, since these subjects showed a relatively larger CTR and relatively lower plasma renin activity (PRA). Interestingly, the PAC/PRA ratio was significantly higher in the HkL subgroup than in the LkL subgroup. This observation supports the idea that an inflated PAC value relative to salt status might be responsible for the pathogenesis of CVD (*8*). Higher potassium might thus be related to the higher PAC/PRA ratio in the HkL subgroup. Therefore, Ald might play a significant role in the pathogenesis of CVD under the more pronounced volume excess in HD patients. It is a critical issue whether a mineralocorticoid receptor antagonist could reduce the prevalence of CVD and improve the survival of the HkL subgroup. Further study is needed to clarify the role of Ald in HD patients, taking into account the nutritional status, the potassium level, and the balance between PAC and sodium status.

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