Author’s response to reviews

Title: The relationship between poor nutritional status and progression of aortic calcification in patients on maintenance hemodialysis

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Dear Editors and reviewers

We sincerely appreciate for the positive consideration of our manuscript entitled “The relationship between poor nutritional status and progression of aortic calcification in patients on maintenance hemodialysis” (BNEP-D-17-00386). We are pleased with the kind comments and suggestions of the reviewers and editors. We attach here our revised manuscript, as well as a point-by-point response to the reviewers’ comments.
Reviewer #1

Thank you for the opportunity to review your manuscript. In general, the topic is quite interesting, and relatively few works have explored the relationship between malnutrition and the development of arterial calcification, moreover with controversial results.

MAJOR COMMENTS:

1. As NF/KDOQI on Dialysis Adequacy and other guidelines recommend a target blood pressure <140/90 mmHg, why did you choose a different value to define "hypertension"?

Response: Thank you for the pointing comment. As reviewer indicated, NF/KDOQI and the Japanese Society of Dialysis Therapy recommend targeting a pre-dialysis BP of less than 140/90 mmHg. However the previous large observational study in Japan revealed that HD patients with intradialytic systolic blood pressure < 140 mmHg had higher mortality. Based on these findings, we start to treat patients with pre-dialytic blood pressure > 150/90 mmHg as hypertension. This is the reason why we defined systolic blood pressure ≥ 150 and/or diastolic blood pressure ≥ 90 mmHg as hypertension. However we changed the definition of hypertension as 140/90 mmHg in order to adapt the standard criteria. This part was revised in the methods section.

Methods section, Patient selection, Page 8, line 131

Hypertension (HTN) was defined as having a systolic blood pressure of ≥140 and/or a diastolic blood pressure of ≥90 mmHg.

2. Moreover, as blood pressure control may be variable in hemodialysis patients, depending upon several factors, why did you take in account just 3 measurements? And at which time point(s) were these ones taken?

Response: Thank you for the comment. Because blood pressures of HD patients fluctuate greatly depending on body fluid volume, home blood pressure measurement is quite important in addition to measurement in hospital. However, we could not address the impact of home blood
pressure due to the limitation of the present study. Instead, we used the mean blood pressure of six dialysis session as a representative value of blood pressure. This part was revised in the methods section. As a result, the prevalence of HTN was changed. The result of multivariate logistic analysis was also changed. We revised Table 2, Fig. 5, and the discussion section.

Methods section, Evaluation of outcome variables, Page 8, line 128

We used the mean blood pressure of six dialysis sessions on the day of blood and serum test as a representative value of blood pressure.

Results section, Independent risk factors for development of high delta-ACI

Page 15, line 227

GNRI < 90 (OR = 4.17; 95% CI = 1.79–9.71), Male sex (OR = 3.29; 95% CI = 1.27–8.53), serum phosphate (OR = 1.71; 95% CI = 1.18–2.47), and HD vintage (OR = 0.99; 95% CI = 0.98–0.99) were selected as independent risk factors for an ACI progression rate greater than the 75th percentile, after accounting for confounders of aortic calcification progression such as age, DMN, current smoking, HTN, i-PTH, and corrected calcium level (Fig. 5).

Discussion section, Page 18, line 271

Furthermore, our results suggested that HD patients with GNRI < 90 had an approximately 4-fold higher risk of rapid aortic calcification progression than those with GNRI ≥ 90.

3. Of course GNRI is a well validated score to assess malnutrition status in the elderly; however, in hemodialysis patient, normalized protein catabolic rate is also very widely used. Why did you choose the first one over the second?

Response: Thank you for the pointing comment. Normalized protein catabolic rate (nPCR) is one of the most important indicators of nutritional status and intake of protein. In our hospital, a regular blood test is conducted every two weeks. Because nPCR requires serum urea nitrogen levels between two consecutive hemodialysis treatments in a week, we could not calculate accurate nPCR. On the other hand, the GNRI requires only serum albumin in single hemodialysis
session. This is the reason why we chose the GNRI as an indicator of nutritional status. However, we agree with the importance of protein intake, and its’ influence on nutritional status. Our next study should address these issues.

Discussion section, Page 21, line 320

Third, we could not address the impact of medications such as phosphate binders, cinacalcet, and antihypertensive drugs, nor of dietary habits and normalized protein catabolic rates, which represent protein intake.

4. 184 hemodialysis patient undergoing abdomen CT scan with 1-year frequency in a single centre is quite a number. What were the main indication for performing these CT scans?

Response: Thank you for the comment. The prevalence of malignancy in HD patients is higher than in healthy individuals. Moreover, patients with acquired cystic kidney disease, particularly those treated with dialysis, have an increased risk of renal cell carcinoma. In Japan, it is common that HD patients undergo screening abdominal CT scans for detecting renal cell carcinoma and other malignancies. This is the main reason for conducting annual CT scans in our hospital. This part was mentioned in the methods section.

Methods section, Patient selection, Page 7, line 114

Almost all patients had undergone annual abdominal computed tomography (CT) scans to detect incidental renal tumor and other malignancies.

5. What were the principal comorbidities (besides diabetes and hypertension) of included patients? And what were the causes of ESRD?
Response: Thank you for the comment. Previous history of cardiovascular diseases such as ischemic heart disease, peripheral arterial disease, and cerebrovascular accident were added in the methods and results section. We divided the cause of ESRD into diabetic nephropathy (DMN) or non DMN (such as autosomal dominant polycystic kidney disease, chronic glomerulonephritis, and others). We added detailed cause of ESRD in the results section.

Methods section, Patient selection, Page 7, line 123

Previous history of CVD was defined as any previous description of ischemic heart disease, cerebrovascular accident, or peripheral arterial disease recorded in the patients’ medical records.

MINOR COMMENTS:

Page 8, line 129: please correct the equation for albumin-corrected-calcium (0.8 factor is missing)

Response: Thank you for the comment. We corrected this part.

Reviewer #2

Dear colleagues, I appreciate the design of your study that adds a contribute to determine risk factors for vascular calcifications in HD patients. Just few questions:

1. Why you write down at the beginning of discussion on line 244 that HD vintage is associated with vascular calcifications if HD vintage was significantly lower in rapidly progressive aortic calcification patients as you underlined in previous sections?
Response: Thank you for the pointing comment. This part was discussed in the discussion section.

Discussion section, Page 19, line 299

On the other hand, the relationship between HD vintage and progression of vascular calcification has been controversial. Previous studies have revealed that dialysis vintage was positively correlated with vascular calcification progression [29, 31]. However, another study demonstrated the converse relationship [32]. In the present study, patients with rapid progression of ACI had significantly shorter HD vintage than those with slow progression (22.5 vs 62.0 months). A previous study demonstrated that the initiation of hemodialysis triggered apoptosis of vascular smooth muscle cell, which induced rapid and extreme vascular calcification [33]. This finding may imply that rapid progression of vascular calcification occurred in the early transition period following initiation of HD.

2. In my opinion it would be interesting to include in baseline variable the dialysis technique (HD, HF, HDF) and the calcium concentration into the dialysis solution used for dialitic treatment, to assess the impact of these factors on vascular calcifications in dialysis patients

Response: Thank you for the comment. We added the modality of hemodialysis in the results sections. Among our study patients, the percentage of patients on HD and those on online hemodiafiltration (OHDF) were 87% and 13%, respectively. Median values of delta-ACIs of patients on HD and those on OHDF are 2.5% and 1.7%, respectively. There was no significant difference in delta-ACI between two modalities (P = 0.323). Because the number of patients on OHDF was much smaller in this study, it was difficult to draw the definitive conclusion of the difference of delta-ACI. However patients on OHDF are increasing in our country, we have the growing interest in differences in cardiovascular events and morbidity between HD and OHDF. Our future study should focus on the difference of progression of vascular calcification in terms of the modality of dialysis. All HD patients in our hospital used same dialysate containing 3.0 mEq/L calcium. This part was added in the methods section.
Between April 2015 and October 2016, we treated 232 patients who had undergone 3–4 h of maintenance HD or online hemodiafiltration using a dialysate containing 3.0 mEq/L calcium three times a week at the Oyokyo Kidney Research Institute in Aomori, Japan.