INTRODUCTION:
Hemodialysis (HD) patients often have a characteristic abnormality of bone metabolism that is known as renal osteodystrophy (ROD). ROD in HD patients with diabetes mellitus is characterized by lower plasma parathyroid hormone levels and a lower bone turnover rate than non-diabetic controls [1]. Bone remodeling is an ongoing cyclical process characterized by two activities: bone formation by osteoblasts and bone resorption by osteoclasts. These two events are normally coupled and interacted to each other. Several studies have showed that bone formation and bone resorption marker well correlate each other in overall HD patients. However, we can obtain no previous study which discusses this correlation within the diabetic HD patients.

In this article, we would like to study the interaction between bone cells by studying the correlation between the specific bone metabolism markers in diabetic patients on regular HD, and also study whether the diabetic patients have some difference in this interaction compared to non-diabetic HD patients.

METHODS:
This cross-sectional study included 128 patients with less than ten years of HD duration whose primary diseases were diabetic nephropathy (DN, N=48) due to type 2 diabetes mellitus and chronic glomerulonephritis (non-DN, N=80). In order to eliminate the influence of HD duration as much as possible, we subdivided the patients into two subgroups: 0–5 HD duration <5 years (0–5y subgroup) and 5 ≤ HD duration ≤ 10 years (5–10y subgroup). We compared the Spearman’s correlation coefficient (r) between high-sensitivity PTH (HS-PTH), bone alkaline phosphatase (BAP), and N-telopeptide of type I collagen (NTx) of the DN group with the non-DN group in the same subgroups (the 0-5y or the 5-10y).

We excluded pre-menopausal female patients to remove the effect of menopause on bone metabolism. None of the female patients underwent hormone replacement therapy with hormones such as estrogens. None of the patients took aluminum hydroxide as a phosphorus binder, steroids, and bisphosphonates. All of the patients received HD three times per week. Blood samples were obtained before dialytic sessions with an overnight fast, and the interval from the last HD session was 72 hours for all patients. Data on the following patients’ characteristic and biochemical parameters were collected from clinical records: gender, age, HD duration, height, body weight, HS-PTH, glucose, calcium (Ca), inorganic phosphate (Pi), magnesium (Mg), aluminum (Al), and β2-microglobulin (β2-m).

Serum BAP was measured as a bone-formation marker and serum NTx was measured as a bone-resorption marker. Enzyme-linked immunosorbent assay (ELISA) kits were used to measure BAP (OSTEOLINKS BAP; Sumitomo Pharmacy Bio Medical) and NTx (OSTEOMARK NTx Serum; Sino-Ostex International) levels according to the manufacturers’ instructions.

RESULTS:
Although the DN group did not have significant correlation between BAP and NTx in the 0-5y subgroup, it had positive correlation which was comparable to that of the non-DN group in the 5-10y subgroup. The DN group had significant correlation between HS-PTH and NTx. In the 0-5y and the 5-10y subgroup, whereas the non-DN group had positive correlation both in these two subgroups. Both of the DN and the non-DN group had positive correlation between HS-PTH and BAP both in the 0-5y and the 5-10y subgroup (Table A, B).

Figure shows the distribution of HS-PTH (a), BAP (b), and NTx (c). In the 0-5y subgroup, the DN group had significantly lower NTx level (Fig. c) and comparable BAP level (Fig. b), compared to the non-DN group. In the 5-10y subgroup, the DN group had comparable NTx level (Fig. c) and significantly higher BAP level (Fig. b), compared to the non-DN group. Although the DN-group had a tendency to have lower HS-PTH level than the non-DN group in both the 0-5y and the 5-10y subgroups, it had no statistical significance (Fig. a).

In glucose, the DN group had significantly higher value than the non-DN group both in the 0-5y subgroup (196.1 ± 53.1 versus 101.1 ± 21.7; p<0.001) and the 5-10y subgroup (111.1 ± 19.2 versus 100.7 ± 15.3; p=0.037) The DN group in the 5-10y subgroup had significantly lower glucose level than in the 0-5y subgroup.

DISCUSSION:
We found the change of correlation between BAP and NTx by prolonged HD duration in the DN group, which might suggest the change of the interaction between osteoblast and osteoclast. Prolonged HD duration is one of the important factors affecting bone metabolism. The incidence of ROD increases with the duration of HD, and long-term HD patients had an increased risk of secondary hyperparathyroidism [2]. There have been few studies about the relation between hyperglycemia and the interaction of bone cells. The previous study reported the important role of sustained high glucose condition itself in osteoclastic bone resorption [3]. Thus, we have two possibilities to explain the change of the correlation between BAP and NTx in the non-DN group. One is that the hyperglycemia since pre-dialysis period impairs the interaction between bone cells, and the interaction recovers with well controlled glycemia. Another is that the interaction between bone cells is seemingly covered by the direct affection of suspended hyperglycemia on bone cells. These two possibilities are both consistent with our result that BAP and NTx correlated to each other in the 5-10y subgroup with well controlled glycemia. We found few previous studies discussed the correlation between glycemic control and bone metabolism markers. Only one paper showed the negative correlation between glycemic control level and the response of osteoblasts and osteoclasts to 1,25(OH)2D3. To ascertain whether hyperglycemia affect the interaction between bone cells, further study is required in the future.

In summary, we studied the interaction between bone cells in the DN group by measuring both BAP as a bone formation marker and NTx as a bone resorption marker. Prolonged HD duration and hyperglycemia could influence this result. The bone metabolism in the diabetic HD patients should be evaluated by both bone formation and resorption markers.

Table: Spearman’s correlation coefficient (r) between serum level of HS-PTH, BAP, and NTx.

<table>
<thead>
<tr>
<th>DN group</th>
<th>non-DN group</th>
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<tbody>
<tr>
<td>HS-PTH</td>
<td>BAP</td>
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<tr>
<td>r</td>
<td>0.631**</td>
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<tr>
<td>BAP</td>
<td>-</td>
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<td>NTx</td>
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Figure: Change of serum HS-PTH, BAP, and NTx by HD duration.

REFERENCES: