Parathyroidectomy and survival among Japanese hemodialysis patients with secondary hyperparathyroidism

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Parathyroidectomy (PTx) drastically improves biochemical parameters and clinical symptoms related to severe secondary hyperparathyroidism (SHPT) but the effect of PTx on survival has not been adequately investigated. Here we analyzed data on 114,064 maintenance hemodialysis patients from a nationwide registry of the Japanese Society for Dialysis Therapy to evaluate the associations of severity of SHPT and history of PTx with 1-year all-cause and cardiovascular mortality. We then compared the mortality rate between 4428 patients who had undergone PTx and 4428 propensity score–matched patients who had not despite severe SHPT. During a 1-year follow-up, 7926 patients of the entire study population died, of whom 3607 died from cardiovascular disease. Among patients without a history of PTx, severe SHPT was associated with an increased risk for all-cause and cardiovascular mortality. However, such an increased risk of mortality was not observed among patients with a history of PTx. In the propensity score–matched analysis, patients who had undergone PTx had a 34% and 41% lower risk for all-cause and cardiovascular mortality, respectively, compared to the matched controls. The survival benefit associated with PTx was robust in several sensitivity analyses and consistent across subgroups, except for those who had persistent postoperative SHPT. Thus, successful PTx may reduce the risk for all-cause and cardiovascular mortality in hemodialysis patients with severe, uncontrolled SHPT.

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Despite considerable advances in dialysis treatment, patients with end-stage renal disease have unacceptably high mortality and cardiovascular morbidity rates worldwide.[1] Secondary hyperparathyroidism (SHPT) is present in the majority of dialysis patients, and its associated disturbances in mineral and bone metabolism are one of the most prominent risk factors for death and cardiovascular events in this population. Observational studies have demonstrated that elevations in serum calcium, phosphorus, and parathyroid hormone (PTH) levels are associated with death and cardiovascular events that are primarily due to vascular calcification.[2–4] Severe SHPT also causes bone pain, muscle weakness, and itching, thus contributing to poor health-related quality of life in dialysis patients.[5–7]

The conventional treatment for SHPT includes phosphate binders and vitamin D receptor activators (VDRAs); however, these treatments do not always provide adequate control of SHPT, particularly among patients with advance parathyroid hyperplasia where the expression of calcium-sensing receptors and vitamin D receptors is reduced.[8,9] Even after the introduction of cinacalcet hydrochloride, there are a proportion of patients in whom SHPT cannot be managed with medical treatment.[10,11] Parathyroidectomy (PTx) is the definitive therapy for treating such uncontrolled SHPT. Successful PTx can drastically lower PTH levels, improve the control of serum calcium and phosphorus levels, and ameliorate symptoms related to SHPT.[5–7,12–14] PTx is thus recommended in international[15] and several national[16,17] practice guidelines when medical treatment fails or is not tolerated because of adverse effects in patients with severe SHPT.

However, whether PTx for severe SHPT improves the survival of dialysis patients has not been adequately investigated. No randomized controlled trials have been conducted to address this issue. Several observational studies have examined the impact of PTx on survival;[18–22] however, these studies were limited by a small sample size, lack of data on biochemical parameters of SHPT, and/or selection of controls without evidence of SHPT. We therefore analyzed nationwide registry data of dialysis patients in Japan to test the hypothesis that PTx improves the survival rate of dialysis patients who have severe, uncontrolled SHPT.

RESULTS

Figure 1 shows the study profile. The final study population consisted of 114,064 patients. The characteristics of the study cohort stratified by categories of intact PTH and history of PTx are shown in Table 1. Overall, the mean age was 63.8 years, the median dialysis duration was 65 months, and 6628 (5.8%) patients had a history of PTx. Among patients without a history of PTx, patients with higher intact PTH were more likely to have longer dialysis duration, have higher serum calcium and phosphorus levels, and receive intravenous VDRAs compared with those with lower intact PTH. Patients who had undergone PTx were more likely to have longer dialysis duration, have lower serum calcium, phosphorus, and intact PTH levels, and were less likely to receive intravenous VDRAs compared with those who had severe SHPT (intact PTH levels >500 pg/ml) but had not undergone PTx.

During a 1-year follow-up, 7926 (6.9%) patients died, of whom 3607 (3.2%) died from cardiovascular disease. Figure 2 shows unadjusted, case-mix-adjusted, and multivariate-adjusted hazard ratios (HRs) of all-cause and cardiovascular mortality associated with categories of intact PTH and history of PTx in the total cohort, considering intact PTH levels of 60 to 180 pg/ml as the reference range. Among patients without a history of PTx, there was a bimodal relationship with a significant increase in the multivariate-adjusted HR of all-cause death associated with intact PTH levels <60 pg/ml (HR, 1.10; 95% confidence interval (CI), 1.04–1.17), 301–500 pg/ml (HR, 1.11; 95% CI, 1.02–1.21), and >500 pg/ml (HR, 1.27; 95% CI, 1.13–1.43). For cardiovascular death, there was a significant increase in the multivariate-adjusted HR for patients with intact PTH levels <60 pg/ml (HR, 1.11; 95% CI, 1.02–1.20) and those with intact PTH levels >500 pg/ml (HR, 1.41; 95% CI, 1.20–1.64). In contrast, such an increased risk of mortality was not observed in patients with a history of PTx, despite the fact that these patients had severe SHPT preoperatively.

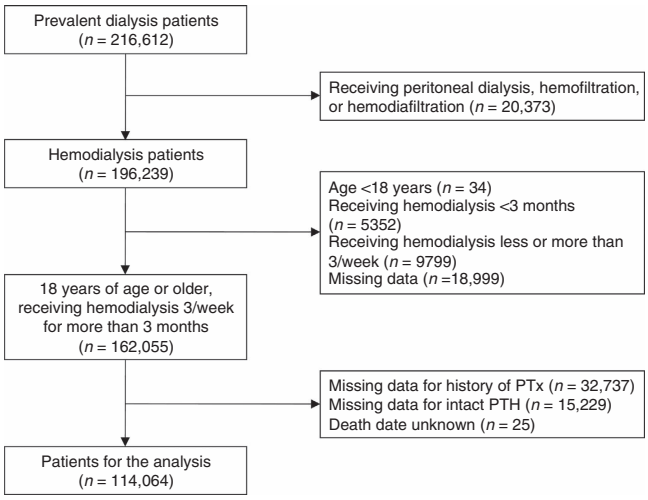

Figure 1 | Study profile. PTH, parathyroid hormone; PTx, parathyroidectomy.

Next, we matched 4428 patients who had previously undergone PTx with 4428 patients who had not undergone PTx, despite severe SHPT, using propensity score matching. The characteristics of the propensity score–matched cohort are shown in Table 2. Distributions of serum levels of intact PTH, calcium, and phosphorus are shown in Figure 3. The two groups of patients were well balanced with respect to age, sex, duration of dialysis, primary cause of renal failure, body mass index, dialysis adequacy (Kt/V), normalized protein catabolic rate, history of cardiovascular disease (myocardial infarction, cerebral infarction, cerebral hemorrhage, and amputation), serum albumin, and C-reactive protein (standardized differences <0.1). Compared with the matched controls, patients with a history of PTx were more likely to have lower levels of serum calcium, phosphorus, and intact PTH and were less likely to receive intravenous VDRAs, representing the effects of PTx.

In the propensity score–matched cohort, the 1-year all-cause mortality was 4.3% ($n=192$) in the PTx group and 6.5% ($n=288$) in the matched control group. The cardiovascular mortality was 1.8% ($n=81$) in the PTx group and 3.1% ($n=137$) in the matched control group. As shown in the Kaplan–Meier survival curves in Figure 4, the PTx group had a significantly lower risk of all-cause and cardiovascular mortality than the matched control group ($P<0.001$ for both). The causes of death and HRs for cause-specific mortality in the PTx group and the propensity score–matched group are shown in Figure 5. Compared with the matched controls, patients who had undergone PTx had a significantly decreased risk of death from heart failure, infectious diseases, and cardiac arrest.

The results of the univariate and multivariable-adjusted survival analyses are shown in Table 3. There was a significantly decreased risk of all-cause and cardiovascular mortality in the PTx group compared with the matched control group in all models. The survival effect of PTx was unaltered by adjustment for VDRA use, but was attenuated by further adjustment for serum calcium and phosphorus, suggesting that these variables may be in the causal pathways that link PTx to outcomes. In the stratified analyses, patients in the PTx group had a significantly decreased risk of all-cause and cardiovascular mortality in many but not all strata, whereas in no stratum was lack of surgery favored (Figure 6). Other propensity score–based approaches, stratification by propensity score and adjustment for propensity score as a covariate, and conventional multivariable Cox regression without using propensity score yielded similar effects of PTx on survival (Table 4).

The survival advantage for the PTx group was qualitatively unchanged when we performed a complete case analysis without imputing missing values (HR, 0.54; 95% CI, 0.38–0.76), when we restricted the study population to a subcohort of patients who were less likely to have significant comorbidity (that is, those <60 years old, without diabetes as a primary cause of renal failure, and with no history of CVD) (HR, 0.51; 95% CI, 0.31–0.84), when we excluded