Hypercalcaemia is associated with poor mental health in haemodialysis patients: results from Japan DOPPS

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Abstract

Background. The Dialysis Outcomes and Practice Patterns Study (DOPPS) reported high incidence of depression in haemodialysis patients. Hypercalcaemia and high parathyroid hormone (PTH) levels are aetiological factors of psychological disorders. We examined the association between mineral metabolism abnormalities and mental health in Japanese-DOPPS patients.

Methods. We used baseline data of Japan-DOPPS, Phase 1 (2755 patients, 1999–2001) and Phase 2 (2286 patients, 2002–03). The outcome variable was mental health using the mental health domain of SF-36. We examined the association between serum corrected calcium, phosphorus, calcium × phosphorus product and intact PTH concentrations, and mental health using analysis of covariance and also the associations between corrected calcium levels and current use of vitamin D and calcium-containing phosphate binder.

Results. There was a significant association between mental health and corrected calcium levels. A significantly lower mental health score was noted in patients with corrected calcium ≥11 mg/dl than in <8.4 (P = 0.04), ≥8.4 to <10.2 (P = 0.009) and ≥10.2 to <11 mg/dl (P = 0.003). The association was significant even after adjustment for age, sex and other confounders. However, there was no relationship between intact PTH and mental health. High-corrected calcium levels were significantly associated with the use of intravenous active vitamin D and calcium-containing phosphate binder.

Conclusions. Hypercalcaemia, but not high intact PTH, is associated with poor mental health in dialysis patients. While a cause–effect relationship between hypercalcaemia and deterioration of mental health needs further confirmation by longitudinal and prospective studies, our observational findings suggest the importance of control of serum calcium concentration in dialysis patients.

Keywords: DOPPS; haemodialysis; hypercalcaemia; hyperparathyroidism; mental health

Background

Poor mental health, which includes depressive symptoms and depression, is a major public health problem and the most frequent group of psychological problems in haemodialysis patients [1–4]. Recent studies reported that among haemodialysis patients, those with depressive symptoms were at higher risk of death, higher risk of hospitalization and had higher rates of dialysis withdrawal than those without depressive symptoms [5,6].

Depression is also a major symptom in patients with primary [7] and secondary [8] hyperparathyroidism. Massry [9] indicated that the parathyroid hormone (PTH) has uraemic effects on multiple organs, which lead to the development of neurotoxicity in the central and peripheral nervous systems, in patients with end-stage renal disease (ESRD) [9]. Driessen et al. [8] reported that patients with secondary hyperparathyroidism and depression have significantly elevated serum PTH levels.

On the other hand, dialysis patients, who are often treated with active vitamin D or calcium preparations,
sometimes develop hypercalcaemia [10–13]. Hypercalcaemia per se is known to result in psychoneurological symptoms such as delirium [14–16]. Although hypercalcaemia and high PTH levels are the aetiological factors for psychoneurological symptoms, the exact role of these factors in the pathogenesis of mental disorders in haemodialysis patients is not clear at present.

In the present study, we examined the associations between serum corrected calcium, phosphorus and intact PTH concentrations with mental health status in haemodialysis patients.

**Methods**

This cross-sectional research was conducted using baseline data from the Dialysis Outcomes and Practice Patterns Study (DOPPS) [5,17], a multicentre, cohort study conducted in North America, Europe and Japan. Subjects of this study were restricted to those Japanese who lived in Japan (the data from the ‘Japan-DOPPS’). The research protocol was approved by the research committees of institutions participating in Japan-DOPPS. In Japan-DOPPS, Phase 1 was conducted between 1999 and 2001 (2755 patients) and Phase 2 between 2002 and 2003 (2286 patients) as two independent studies.

The methods used for collection of data for DOPPS have been described in detail in previous reports [5,17]. In Japan-DOPPS, dialysis centres in Japan were randomly sampled to represent the entire country and 20–40 patients randomly selected from each centre were registered with the DOPPS and followed-up for up to 3 years (Phase 1) or 2 years (Phase 2). At registration to Phase 1 and Phase 2, the study coordinators extracted the following data from the medical records as baseline characteristics: age, sex, duration of dialysis, medications used, clinical laboratory data [e.g. total calcium (mg/dl), intact PTH (pg/ml), phosphorus (mg/dl), albumin (g/dl), haemoglobin (g/dl)], comorbidity [coronary heart disease, congestive heart failure, hypertension, other cardiovascular diseases, cerebrovascular diseases, diabetes mellitus, cancer, gastrointestinal (GI) bleeding, human immunodeficiency virus (HIV) infection, lung diseases, neurological diseases, peripheral vascular diseases and recurrent cellulites] and history of parathyroidectomy (PTX).

In Phase 2 of DOPPS, to determine the factors that could contribute to hypercalcaemia in haemodialysis patients, the use of medications was investigated by asking the following questions: (i) Has the patient received intravenous vitamin D or vitamin D analogue(s) for the control of serum PTH level within one week before the date of the questionnaire? (ii) Has the patient received a calcium-containing phosphate binder within one week before the date of the questionnaire? (Table 1).

In addition to the medical records, in both phases of the study, the Japanese version of self-report, health-related quality of life (QOL) questionnaire (SF-36 Health Survey, hereafter SF-36) was distributed to patients for response. The SF-36 is a QOL scale that permits quantitative evaluation of subjective health status and its impact on daily function and social function. The SF-36 consists of 36 questions and when all questions are answered, a score ranging from 0 to 100 is calculated for each of the eight domains (e.g. physical function, mental health, social function, role-physical, role-emotional, bodily pain, general health and vitality). A low mental health score represents poor mental health. Previous studies showed that the mental health domain of SF-36 could be used as a screening tool for depressive state [18]. Furthermore, the SF-36 has been validated not only for the Japanese general population [19], but also for dialysis patients [20]. Patients who were unable to complete the questionnaire, such as those with ostensible cognitive deficits, were excluded.

Corrected calcium concentration was calculated using the following formula: Corrected calcium = total calcium (mg/dl) + 4 – albumin (g/dl). The outcome of this research was mental health (score 0–100) as a continuous variable. Then, we examined the association between serum corrected calcium, phosphorus, intact PTH concentrations and Ca x P product and SF-36 mental health score.

**Statistical methods**

Data are expressed as mean ± SD unless otherwise stated. We examined the correlations between serum corrected calcium, phosphorus and intact PTH concentrations, with mental health. In this study, pooled data from Phase 1 and Phase 2 studies from Japan-DOPPS were analysed. Based on the Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines [21], serum corrected calcium, phosphorus and intact PTH concentrations were categorized by the following cut-off concentrations: serum corrected calcium: 8.4, 10.2 and 11.0 mg/dl, phosphorus: 2.5, 3.5 and 5.5 mg/dl, and intact PTH: 150, 300 and 600 pg/ml. Cut-off points of Ca x P product were defined based on 25, 50 and 75 percentiles of Ca x P product levels. First, we examined the correlations between corrected calcium, phosphorus, intact PTH concentrations and Ca x P product levels, with mental health scores from the SF-36 using analysis of variance (crude analysis). Then, analysis of covariance was used to examine the associations with adjustment variables. In this analysis,
Results

Of 5041 patients with pooled data from Phase 1 and 2 studies, 4115 responded to the mental health questions on the SF-36 and were included in the calculation of mental health scores. The baseline characteristics are listed in Table 2. The mean age of 4115 patients of Phase 1 and 2 studies was 58.2 ± 12.4 and 60.9 ± 12.9 years, respectively, and males formed 63 and 61%, respectively, of the population. The duration of dialysis was less than 6 months in 757 patients. Furthermore, 58% of the patients used vitamin D preparations and 79% used calcium-containing phosphate binders.

Figure 1 shows the results of analysis of variance (crude analysis). As shown in Figure 1A, 64.0% of patients had the target serum calcium levels, 15.4% had less, and 20.6% had more than that. Furthermore, 40.8% of patients had the target serum phosphorus levels, 6.0% had less and 53.2% had more than the target (Figure 1B). As shown in Figure 1C, 26.1% of patients had target serum intact PTH levels, 51.4% had less and 19.5% had more than that. The mean mental health scores of the group with corrected calcium levels of <8.4 mg/dl and ≥8.4 to <10.2 mg/dl, ≥10.2 to <11.0 mg/dl and ≥11.0 mg/dl were 64.1 [95% confidence interval (CI): 62.2–66.1], 64.3 (95%CI: 63.4–65.2), 65.6 (95%CI: 63.6–67.6) and 58.9 (55.9–61.9), respectively. The group with corrected calcium levels ≥11.0 mg/dl had a significantly lower mental health score than that with <8.4 mg/dl. The difference was 5.2 points (P = 0.04) and its effects size (ES) was 0.22. Similarly, the group with corrected calcium levels ≥11 mg/dl had a significantly lower mental health score than that with levels ≥8.4 to <10.2 mg/dl, and the group with ≥10.2 to <11.0 mg/dl. The differences were 5.4 points (P = 0.009) and 6.7 points (P = 0.003), respectively, and their ESs were 0.25 and 0.31, respectively. Even after adjustment for age, sex, serum albumin concentration, haemoglobin, serum phosphorus concentration, use/non-use of vitamin D preparation, use/non-use of calcium-containing phosphate binder, presence/absence of comorbidity (13 variables) and history of PTX, the differences between the group with corrected calcium levels ≥11.0 mg/dl and groups with ≥8.4 to <10.2 mg/dl and ≥10.2 to <11.0 mg/dl were still significant (Table 3). That is, the mental health score of patients with corrected calcium levels of ≥11.0 mg/dl was 5.0 (95% CI: 0.5–9.6) points lower than that of the group with ≥8.4 to <10.2 mg/dl and 6.6 (95% CI: 1.6–11.8) points lower than the group with ≥10.2 to <11.0 mg/dl. On the other hand, there were no associations between serum phosphorus, intact PTH and Ca × P product and mental health by crude analysis (Figure 1B–D) and multivariate analysis (data not shown).
Table 1 shows the distribution of patients categorized by corrected calcium levels according to the use/non-use of intravenous vitamin D or its analogue for control of PTH and calcium-containing phosphate binder within one week of the investigation date. The percentage of patients receiving intravenous active vitamin D preparations or calcium-containing phosphate binder was significantly higher in dialysis patients with hypercalcaemia than those without ($P < 0.0001$).

**Discussion**

Depressive symptoms and depression are major public health problems and the most frequent psychological problems reported in haemodialysis patients [1–4], probably because these patients perceive having a terminal disease (ESRD) without the possibility of recovery, the need for frequent treatment and presence of serious ESRD-related complications. Our results showed significantly lower mean mental health scores...
Analysis was conducted by multiple comparison test followed by Bonferroni test. Corrected Ca, phosphorus and PTH.

Adjustment variables: age, sex, duration of dialysis, albumin, haemoglobin, Vitamin D, PhosBinder, comorbidity (13 variables), PTX.

These observations were made in a small-study population [7–9, 24–27]. Our study, however, showed no evidence of PTH involvement in mental health deterioration. This might be due to the small population sample (145 patients, 3.5%) of patients with severe secondary hyperparathyroidism (intact-PTH >600 pg/ml) in our study. Further research is required to draw definitive conclusions on the relationship between PTH and mental health in dialysis patients.

The K/DOQI guideline [21], detailing the goals of treatment of abnormal bone mineral metabolism in dialysis patients, was established in 2003. In Japan, only 9% of dialysis patients achieve all the goals for serum calcium, phosphorus and PTH [28]. The percentage of patients achieving the goal for serum corrected calcium is especially low (49%), and 14% of dialysis patients have hypercalcaemia (serum calcium >10.2 mg/dl) [28]. In our study, hypercalcaemia (serum calcium ≥10.2 mg/dl) was noted in 677 (16.5%) of the 4115 patients. Of these, 5.0% (204/4115 patients) had severe hypercalcaemia (serum calcium ≥11.0 mg/dl). These findings suggest that many dialysis patients with persistent hypercalcaemia are provided with long-term treatment with active vitamin D preparations or calcium salts to reduce PTH and phosphorus levels in clinical settings. Our finding of the potential negative impact of hypercalcaemia on mental health emphasizes the importance of careful management of serum calcium, phosphorus and PTH concentrations.

**Limitation**

This study is cross-sectional research. Our results should be viewed cautiously for three reasons. First, in this study, we used the mental health domain score of the SF-36 as mental health state, but not depressive state. Therefore, if the subjects had a low mental health score, we considered them in poor mental health but not in depression. Second, the SF-36 was developed for comparing the health status of different groups rather than individuals [29]. It is therefore difficult to discuss...
the impact of low mental health domain score of the SF-36 in each individual. For this reason, the clinical significance of the effect of changes in serum calcium concentration on mental health should be further examined. Third, we analysed the data using a multivariate model that included haemoglobin as a parameter of iron status and albumin as a marker of nutritional status. Previous studies showed the association between haemoglobin and depressive symptoms. Although haemoglobin concentration does not always correlate with iron status, it is one of possible surrogates for iron status. Although albumin is in fact not an appropriate marker for nutritional status, no other appropriate markers of nutritional status were available for analysis. Moreover, three PTH assay methods were available in Japanese haemodialysis centres. Although the normal ranges of serum intact PTH concentrations of these PTH assays are almost the same (10–72 pg/ml), we cannot exclude possible influence of the assay method on the reported results.

Conclusions

In this study, we found a possible association between hypercalcaemia and poor mental health in dialysis patients. Our study also shows that treatment with intravenous active vitamin D preparations and/or oral calcium salts is responsible for the development of hypercalcaemia in dialysis patients. While a cause–effect relationship between hypercalcaemia and deterioration of mental health needs further confirmation through longitudinal studies as well as prospective randomized studies, our observational findings suggest the importance of control of serum calcium concentration in dialysis patients treated with active vitamin D preparations or calcium salts.

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Conflict of interest statement. None declared.

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