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# The effects of percutaneous ethanol injection on secondary hyperparathyroidism in chronic renal failure patients; a before-and-after study

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**ABSTRACT**

**Introduction:** Parathyroidectomy is the only curative treatment for primary hyperparathyroidism and is required in approximately 10% of dialysis patients with secondary or tertiary hyperparathyroidism. This study aims to evaluate the effectiveness and safety of percutaneous ethanol injection therapy (PEIT) in patients with treatment-resistant hyperparathyroidism associated with renal failure.

**Methods:** In this before-and-after study, nine patients with chronic renal failure who met the indications for parathyroidectomy were enrolled. Parathyroid lesions were localized using Sestamibi scintigraphy, and all participants underwent ultrasonography-guided injections of 96% ethanol into the identified parathyroid glands. Parathyroid function tests and other biochemical markers were measured before the procedure and one month after the intervention.

**Results:** Nine patients with renal failure and hyperparathyroidism were evaluated, including six males and three females. The mean age was 45.44 years, and the mean duration of hemodialysis was 12 months. One month after ethanol injection, the Wilcoxon signed-rank test showed a statistically significant reduction in PTH levels ($P = 0.01$), with a large effect size of 0.867. However, likely due to the short follow-up period and the gradual nature of calcium fluctuations, no significant changes in serum calcium levels were observed ($P = 0.374$).

**Conclusion:** Based on the results, PEIT can be an acceptable treatment for secondary hyperparathyroidism in chronic renal failure, reducing PTH levels with minimal complications.

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## Introduction

In patients with chronic dialysis, increases in parathyroid mass result from either polyclonal proliferation of parathyroid cells (e.g., diffuse hyperplasia) or monoclonal expansion (e.g., adenoma) (1). In end-stage renal disease, diffuse parathyroid hyperplasia is typically triggered by hypocalcemia, hyperphosphatemia, or calcitriol deficiency (2). Conversely, treatment-resistant

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hyperparathyroidism often develops due to monoclonal expansion or adenomatous transformation driven by somatic mutations (3). Parathyroidectomy, the surgical removal of one or more parathyroid glands, remains the definitive treatment for primary hyperparathyroidism. Despite advances in medical therapies over the past two decades, approximately 10% of chronic dialysis patients with secondary or tertiary hyperparathyroidism still require parathyroidectomy (4,5). The incidence of parathyroidectomy for refractory hyperparathyroidism in dialysis patients is approximately 7 to 10 per 1000 patient-years (6). Tertiary hyperparathyroidism is clinically defined by elevated parathyroid hormone (PTH) levels accompanied by hypercalcemia in patients undergoing chronic dialysis (7). One of the significant challenges faced by nephrologists in managing chronic kidney failure is controlling the rise in PTH during dialysis and after kidney transplantation (8,9). Parathyroidectomy is indicated for tertiary hyperparathyroidism in chronic dialysis patients with PTH levels exceeding 800 pg/mL despite optimized treatment with calcium and active vitamin D, with symptoms such as severe hypercalcemia, progressive bone disease, pruritus, calciphylaxis, or myopathy warranting intervention (10). Some authors suggest that parathyroidectomy may be warranted in asymptomatic dialysis patients with treatment-resistant hyperparathyroidism when PTH levels exceed 1000 pg/mL (10). Persistent hyperparathyroidism after surgery may result from residual parathyroid tissue left behind following partial parathyroidectomy or total parathyroidectomy with autografting. In rare cases, an ectopic gland that was not identifiable due to the activity of other hyperfunctioning glands may subsequently increase in size and activity (2,11). When relapse occurs, PTH levels rise sharply, leading to substantial skeletal and cardiovascular complications, and treatment options in these situations remain limited. These persistent nodules are typically resistant to medical therapy because of reduced calcium and calcitriol receptor expression (2). In 1998, more than 600 patients in Japan underwent percutaneous ethanol injection therapy (PEIT) into the parathyroid glands (12). Although various effective interventions have been explored in recent years, a considerable number of patients continue to experience uncontrolled metabolic abnormalities, ultimately requiring parathyroidectomy. Given that PEIT is significantly less invasive than parathyroidectomy and has not been extensively studied in Iran for the treatment of refractory hyperparathyroidism in dialysis patients, this study aims to evaluate the therapeutic efficacy of PEIT in hemodialysis patients with renal failure.

## Materials and methods

### *Study Design and Participants*

In this prospective before-and-after study, patients with chronic renal failure attending the dialysis unit at Imam Reza Hospital were evaluated by both an endocrinologist and a nephrologist to identify individuals meeting the inclusion criteria. Ultimately, nine patients were enrolled. All participants were on chronic hemodialysis and had indications for parathyroidectomy, defined by PTH levels exceeding 800 pg/mL despite adequate calcium supplementation and active vitamin D therapy, along with clinical features such as hypercalcemia, progressive bone disease, pruritus, calciphylaxis, or severe myopathy. In addition, asymptomatic dialysis patients with treatment-resistant hyperparathyroidism (PTH > 1000 pg/mL) despite appropriate calcium and active vitamin D administration during the preceding six months were also included. Before enrollment, all eligible patients received comprehensive information regarding the study protocol, including the potential risks and benefits of PEIT for secondary hyperparathyroidism. Alternative therapeutic options, such as surgical parathyroidectomy, were thoroughly explained, including their potential advantages (e.g., definitive removal of hyperplastic glands), risks (e.g., postoperative hypocalcemia or recurrent laryngeal nerve injury), and clinical indications. The study protocol was approved by the Ethics Committee of Mashhad University of Medical Sciences (IR.MUMS.MEDICAL.REC.1399.357), and written informed consent was obtained from all participants.

### *Clinical sample collection and analysis*

Demographic information and clinical and paraclinical findings—including CKD etiology, past medical history (such as diabetes mellitus, hypertension, and bone disorders), type and duration of dialysis, parathyroid function tests, serum calcium, albumin, phosphorus, 25-OH vitamin D levels, parathyroid imaging findings (ultrasonography and Sestamibi SPECT/CT indicating adenoma or hyperplasia and unilateral

or bilateral involvement), and the medications used (including calcium carbonate, calcitriol, cinacalcet, and sevelamer)—were recorded using a structured data collection checklist. For ultrasonography guidance, a SonoSite M-Turbo machine equipped with a 13.6 MHz linear probe was used. After skin sterilization and without local anesthesia, a 25-gauge needle was inserted into the adenomatous or hyperplastic gland under real-time ultrasonography guidance. The lesion had previously been localized using sestamibi parathyroid scintigraphy. Sestamibi parathyroid scanning is a nuclear imaging modality used to localize parathyroid adenomas, a common cause of hyperparathyroidism (13). Based on the estimated volume of the adenoma or hyperplastic gland using the three-dimensional ultrasonographic method, 1–4 mL of 96% ethanol was injected into the targeted parathyroid lesion, and ethanol diffusion was monitored by ultrasonography. Levels of PTH, calcium, phosphorus, albumin, blood urea nitrogen (BUN), and creatinine were measured before the procedure and one month after the intervention. Throughout the follow-up period, any complications related to the intervention were carefully assessed.

### *Data analysis*

All statistical analyses were performed using Jamovi software (14–16). The Shapiro–Wilk test was used to assess data normality before and after PEIT. Because the variables were not normally distributed, differences in biomarker levels before and after treatment were analyzed using the Wilcoxon signed-rank test for paired continuous variables. The rank-biserial correlation was calculated to determine the effect size for significant nonparametric differences. A significance level of 0.05 was applied to all analyses.

## Results

The study included data from nine hemodialysis patients with chronic kidney disease (CKD), consisting of six males and three females. The mean age of the patients was 45.44 ± 12.33 years (range: 30–62 years). The average duration of hemodialysis was 12 months. The characteristics of the participants' parathyroid lesions are presented in Table 1.

**Table 1.** Parathyroid lesion features.

| | | | | | |
|---|---|---|---|---|---|
| Hyperplasia* | 7 (77.8) | Single | 1 (11.1) | Unilateral | 2 (22.2) |
| Adenoma* | 2(22.2) | Multiple | 8(88.9) | Bilateral | 7 (77.8) |

*n(%)

The mean vitamin D level among the patients was 41.31 ng/mL. Maintaining adequate vitamin D levels is essential for individuals with CKD. The distribution of underlying CKD etiologies varied among the participants: three patients had congenital kidney disease, three had hypertension, and three had membranous glomerulonephritis. Additionally, one patient had diabetes mellitus as a comorbid condition. Reported complications following the injections included pain in two patients; pain accompanied by a foreign-body sensation in three patients; pain with a change in voice in one patient; and an isolated foreign-body sensation in one patient. Table 2 presents the changes in biomarker levels observed one month after PEIT. Using Jamovi, the Shapiro–Wilk test indicated that the variables did not follow a normal distribution. Consequently, the Wilcoxon signed-rank test demonstrated a statistically significant reduction in PTH levels (P = 0.01), with a large effect size of 0.867. The rank-biserial correlation, an effect size for nonparametric differences, further underscored the clinical relevance of this reduction. Furthermore, nuclear parathyroid scans (Tc-99m sestamibi SPECT/CT) showed no detectable changes in any of the patients following treatment.

**Table 2.** Biomarker changes, 1 month after PEIT.

| Variable | Before/After | *p*-value* |
|---|---|---|
| PTH (pg/mL) | 2078(757)/1350(354) | 0.010 |
| Ca (mg/dL) | 8.713 (0.544)/8.900 (0.742) | 0.374 |
| P (mg/dL) | 5.788 (0.897)/5.188 (0.700) | 0.313 |
| BUN (mg/dL) | 68.250 (31.671)/63.333 (16.967) | 0.917 |
| Cr (mg/dL) | 9.357 (1.037)/8.325 (1.417) | 0.144 |

*Resulted from the Wilcoxon signed-rank test for paired continuous variables.
Abbreviations: PEIT, percutaneous ethanol injection treatment; PTH, parathyroid hormone; Ca, Calcium; P, phosphorus; BUN, blood urea nitrogen; Cr, creatinine.

## Discussion

The findings of this study underscore the potential effectiveness of PEIT in managing hyperparathyroidism among patients with chronic renal failure. Our results demonstrated a statistically significant reduction in PTH levels following percutaneous ethanol injection. PEIT has been proposed as a viable alternative to surgery in this patient population, providing a relatively rapid and safe therapeutic option for severe secondary hyperparathyroidism in various clinical contexts. Although successful ablation of hyperfunctioning

nodules depends on several factors, a comprehensive, standardized definition of eligibility criteria for PEIT therapy has yet to be established (17,18). These findings are consistent with previous studies reporting the beneficial effects of PEIT in the management of hyperparathyroidism. PEIT is effective in dialysis patients as well as in kidney transplant recipients, particularly in cases involving high surgical risk or resistant hyperparathyroidism (11,19). Douthat et al. demonstrated that intact PTH (iPTH) and calcium levels remained reduced at the final follow-up after PEIT, and that mean serum alkaline phosphatase levels decreased significantly within 1–7 days following treatment, supporting the potential utility of PEIT in kidney transplant recipients (11). Tanaka et al. evaluated the efficacy of PEIT for secondary hyperparathyroidism in hemodialysis patients. They reported that PEIT is a safe and effective intervention for reducing PTH levels, particularly in individuals with 1 or 2 enlarged glands (20). Similarly, Yazdani et al. showed that ultrasound-guided ethanol injection is effective for managing primary hyperparathyroidism and is a viable alternative for patients who are not surgical candidates, with a favorable safety profile and no significant complications when performed by experienced practitioners (21).

## Limitations

One of the limitations of this study was its small sample size, despite the inclusion of patients with diverse demographic characteristics, hyperparathyroidism types, and etiologies. This diversity may enhance the generalizability of the findings and suggest potential applicability across different patient groups. In primary hyperparathyroidism, reduced bone mineral density (BMD) is considered an independent indication for parathyroidectomy. However, in dialysis patients, the situation differs because renal osteodystrophy is multifactorial. In the present study, BMD was not assessed, as osteoporosis alone—without a giant bone cyst or fracture—does not alter the indication for parathyroidectomy in secondary hyperparathyroidism in patients with end-stage renal disease (ESRD) according to ESRD guidelines. Nonetheless, given the high prevalence of osteoporosis and fractures in dialysis patients, some experts recommend DXA scanning as an essential tool for monitoring bone loss in this population (22). Due to incomplete albumin data and the inability to calculate corrected calcium levels, the before-and-after comparison was performed using serum calcium levels, consistent with previous studies (23). Another limitation of this study is the short follow-up duration of one month, which prevented evaluation of long-term outcomes. Future studies with extended follow-up periods are required to address this limitation. Additionally, the non-normal distribution of the data, potentially due to the small sample size, may have reduced the analyses' statistical power.

## Conclusion

Our findings suggest that PEIT may serve as a viable therapeutic option for secondary hyperparathyroidism, effectively reducing PTH levels in chronic renal failure patients without causing major complications. Future studies with larger sample sizes and the inclusion of additional biochemical and clinical markers are needed to provide a more comprehensive understanding of its therapeutic impact.

## Ethics approval and consent to participate

The study was approved by the Ethics Committee of the Mashhad University of Medical Sciences (IR.MUMS.MEDICAL.REC.1399.357). All participants provided informed consent to participate in the study.

## Consent for publication

Not applicable.

## Availability of data and materials

The datasets analyzed during the current study are available from the corresponding author at reasonable request.

## Competing interests

The authors declare that they have no competing interests.

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## Authors' contributions

Z.G and M.M. formulated the research question and designed the study; N.M., M.P.R. and F.H. performed the statistical analysis; Z.M., F.N., and V.D.K conducted the data interpretation and discussion; S.S. and S.H. drafted the manuscript. All authors read and approved the final manuscript.

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