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Parathyroid Hormone Replacement Therapy in Hypoparathyroidism: A Meta-Analysis

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Key words
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calcitriol
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bone mineral density

Abstract
This study investigated the effect of human parathyroid hormone replacement therapy on specific disease-related outcomes in patients with hypoparathyroidism. Medline, Cochrane, EMBASE, and Google Scholar databases were searched until January 13, 2015 for randomized trials using the following search terms: hypoparathyroidism, parathyroid hormone/PTH, and hormone replacement therapy. Five randomized controlled trials (n = 245) that investigated effect of either PTH (1–34) (3 trials) or PTH (1–84) (2 trials) on serum calcium, phosphate, 1, 25-dihydroxyvitamin D, 25-dihydroxyvitamin D levels, and urine level of calcium were included in the meta-analysis. Both PTH (1–34) and PTH (1–84) therapies were not associated with change in serum calcium level compared with calcitriol/placebo. The level of 24-h urine calcium excretion had a significant decrease in PTH (1–34)-treated group compared placebo/calcitriol (control) group (p ≤ 0.012). PTH (1–34) did not change serum phosphate (p = 0.053). PTH (1–84) did not change level of 24-h urine calcium excretion compared with control (p ≥ 0.214) but it did decrease the levels of serum phosphorous (p = 0.000). Both PTH-replacement therapies were not associated with change in serum 1,25-dihydroxyvitamin D level compared with control (p ≥ 0.606), but were associated with a significant decrease in serum 25-dihydroxyvitamin D levels (p ≤ 0.04). In conclusion, although the number of randomized trial is limited, our meta-analysis suggests that PTH (1–34) replacement therapy may maintain the serum calcium levels in the normal range by reducing the levels of urine calcium excretion, and both replacement therapies may maintain 1,25-dihydroxyvitamin D serum levels by reducing serum level of 25-dihydroxyvitamin D.

Introduction
Hypoparathyroidism is a rare disorder associated with low or absent production of parathyroid hormone (PTH). PTH deficiency results in abnormal mineral homeostasis and is characterized by hypocalcemia, hyperphosphatemia, and hypomagnesemia [1]. In the kidneys, PTH promotes calcium reabsorption, phosphate excretion, and conversion of 25(OH)D by 1α-hydroxylase to 1,25(OH)2D. In the intestines, 1,25(OH)2D enhances the absorption of calcium and, to a lesser degree, phosphate [1]. PTH deficiency disrupts normal mineral homeostasis by lowering intestinal and renal calcium absorption due to reduced renal conversion of 25-hydroxyvitamin D to active 1,25-dihydroxyvitamin D [2–4]. Lack of PTH also decreases bone turnover. A reduction or absence of circulating PTH leads initially to a decrease in bone resorption and then to a coupled reduction in bone formation [2–5]. In adults, the cause of hypoparathyroidism is typically the result of a complication of neck surgery or radiation [2, 3, 6]. Hypoparathyroidism can also result from a number of genetic or autoimmune disorders including familial isolated hypoparathyroidism, DiGeorge syndrome, autoimmune polyendocrine insufficiency type 1 with immune-mediated destruction of the parathyroid glands, and autosomal dominant hypocalcemia resulting from activating mutations in the calcium-sensing receptor [5, 7–10].

The current conventional treatment for hypoparathyroidism is large doses of oral calcium and active vitamin D metabolites or analogues to relieve the symptoms caused by hypocalcemia [11, 12]. However, this approach is not always successful in controlling the disease and precisely controlling serum calcium levels [1, 13, 14]. Short- and long-term complications include large swings in serum calcium levels (hypo or hypercalcaemia) and risk of calcification of the brain, kidney, and other tissues [1, 15].

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Several studies have evaluated the use of hormone replacement therapy in treating hypoparathyroidism using either full-length hormone PTH (1–84) or the biologically active fragment PTH (1–34). Both PTH (1–34) and PTH (1–84) are commercially produced by recombinant DNA technology and are on the market as Forteo® and Natpara®, respectively. All of the clinical studies of PTH (1–34) included in this analysis, however, were performed at the NIH where they used synthetic human PTH (1–34) formulated by the NIH pharmacy [6]. Overall, prior studies investigating the use of PTH-replacement therapy for hypoparathyroidism found that PTH-replacement therapy can maintain normal serum calcium and phosphate levels or reduce the levels of concurrent treatment with calcium and active vitamin D analogues by improving PTH-dependent renal calcium reabsorption or correct diminished bone turnover [1, 5, 6].

In January 2015, PTH (1–84) was approved in the United States by the Federal Drug Administration (FDA) as adjunct therapy to calcium and vitamin D therapy for the control of hypocalcemia in patients with hypoparathyroidism [1]. Therefore, PTH (1–84) (Natpara®) is currently available as an adjunct to conventional therapy for patients who are refractory to calcium and calcitriol alone [1]. Recombinant PTH (1–34) (Forteo®) was approved in 2002 for treatment of severe osteoporosis in adults and, over the past decade, has been used extensively both in Europe and in the US as an off-label replacement therapy for hypoparathyroidism [16]. Toxicology studies in rats found both PTH (1–34) and PTH (1–84) led to dose dependent osteosarcomas in rats [17]. Consequently, both drugs are contraindicated for use in children and the FDA issued a black box warning against use in children [6]. To date, most of the previous studies have been small, which limits the interpretation of some of the findings [6, 18]. In addition, the results for renal calcium excretion and phosphate levels have been variable [6]. This study investigated the effect of human parathyroid hormone replacement therapy on specific disease-related outcomes, including serum and urine calcium levels, serum phosphate levels, and levels of 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D in patients with hypoparathyroidism.

Materials and Methods

Search strategy

This meta-analysis was performed in accordance with PRISMA guidelines. Medline, Cochrane, EMBASE, and Google Scholar databases were searched until January 13, 2015 using the following search terms: hypoparathyroidism, parathyroid hormone/PTH, hormone replacement therapy, vitamin D, calcitriol, and calcium. Randomized controlled trials (RCTs) and 2-arm, nonrandomized prospective studies, which investigated treatment in patients who had chronic hypoparathyroidism ≥ 18 months were included. All included studies had to quantitatively report the outcomes of interest. Retrospective studies, cohort studies; letters, comments, editorials, case report; proceeding, and personal communications were excluded. The lists of potential studies were hand searched by 2 independent reviewers, and if necessary, a third reviewer was consulted to resolve any discrepancies regarding study eligibility.

Data extraction

The following information/data was extracted from studies that met the inclusion criteria: the name of the first author, year of publication, study design, number of participants in each group, participants’ age and gender, intervention, and outcomes (e.g., serum calcium levels, 24-h urine calcium level, serum phosphate level, and serum 25-dihydroxyvitamin D and 1,25-dihydroxyvitamin D levels).

Quality assessment

The quality of each included study was assessed using the Cochrane Collaboration’s tool for assessing risk to assess the included studies [19]. Two reviewers assessed the quality of the studies and a third was consulted for solving any discrepancies.

Statistical analysis

The primary outcome was serum calcium levels and 24-h urine calcium levels. Secondary outcomes were levels of serum phosphorous, 1,25-dihydroxyvitamin D, and 25-hydroxyvitamin D. Standardized difference in means (or so called standard mean difference) was used as the index of effect size that represented the effect of PTH-replacement therapy in the treatment of hypoparathyroidism. Heterogeneity was assessed by Cochran’s Q statistic and I². Cochran’s Q statistic was defined as the weighted sum of the squared deviations of the estimates of all studies and I² indicated the percentage of the observed between-study variability caused by heterogeneity. Either the Q statistic with p < 0.1 or I² > 50% was considered indicative of heterogeneity. If heterogeneity existed, standardized difference in means of selected studies was pooled under random effect model using the DerSimonian-Laird approach. Otherwise, the fixed-effects model (Mantel-Haenszel approach) was used. Sensitivity analysis was performed by the leave-one-out approach. A 2-sided p-value < 0.05 was considered statistically significant. Publication bias was not evaluated as at least 5 studies are necessary for this analysis [20]. All statistical analyses were performed using Comprehensive Meta-Analysis, version 2.0 (Biostat, Englewood, NJ, USA).

Results

The initial search identified 181 potential studies of which 161 were excluded for not being relevant (Fig. 1). After a complete full-text review of the remaining 20 studies, 15 were eliminated.
for not reporting the outcomes of interest quantitatively (n = 12), being single-arm studies (n = 2), and being a repeated study of an included RCT (n = 1).

Five studies were included finally in the meta-analysis [13, 14, 16, 19, 20]. Winer et al. [18] reported the findings from a 3-year long-term randomized, parallel group, open-label study, of which a number of the participants (21/27) were recruited from previous RCTs from the same research group [21, 22]. In the study of Winer et al. (2003) [18], only 6 subjects had not been exposed to PTH therapy.

Four studies were randomized controlled studies [13, 14, 16, 18] and one study was a randomized crossover trial [20] (Table 1). Two of the 4 studies investigated the effect of PTH (1–84) compared with placebo [13, 14], and the other 3 studies evaluated the effect of PTH (1–34) compared with calcitriol (1,25-dihydroxyvitamin D) [16, 18, 21]. All subjects also received calcium, vitamin D, or α-calcidol/calcitriol/ergocalciferol as dietary supplement. Together the 5 studies included 245 subjects. Across the studies, the mean duration of disease ranged from 8–17 years, and the mean follow-up time was from 10 weeks to 3 years. The mean age of participants ranged from 8.8 to 53 years of age. One long-term randomized, parallel group, open-label study was specifically designed for pediatric patients (age 5–14 years) [16]. The studies of Winer et al. (2010) [16] and Winer et al. (1996) [21] consisted mostly of males (60–71 %), while those of Sikjaer et al. (2011) [14], Winer et al. (2003) [18], and Mannstadt et al. (2013) [13] primarily recruited females (71–90 %).

Table 1 Summary of basic characteristics of selected studies for meta-analysis.

<table>
<thead>
<tr>
<th>Study</th>
<th>Study design</th>
<th>Interventions</th>
<th>Supplement treatment</th>
<th>Number of patients</th>
<th>Age (years)</th>
<th>Male (%)</th>
<th>Duration of disease (years)</th>
<th>Follow-up time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Winer et al. 2010 [16]</td>
<td>RCT</td>
<td>PTH (1–34)</td>
<td>Combined calcium and cholecalciferol</td>
<td>7</td>
<td>10.2 (2.3) b</td>
<td>60</td>
<td>n/a *</td>
<td>3 years</td>
</tr>
<tr>
<td>Winer et al. 2003 [18]</td>
<td>RCT</td>
<td>PTH (1–34)</td>
<td>Calcium</td>
<td>14</td>
<td>38 (18–70)</td>
<td>29</td>
<td>12 (1–35)</td>
<td>3 years</td>
</tr>
<tr>
<td>Winer et al. 1996 [21]</td>
<td>Randomized Crossover Trial</td>
<td>PTH (1–34)</td>
<td>None</td>
<td>10</td>
<td>45.5 (14.5)</td>
<td>60</td>
<td>17 (2, 41) b</td>
<td>10 weeks</td>
</tr>
</tbody>
</table>

*Data were shown by mean (SD)

bShown by median (range)

●▶

The pooled standardized difference in mean serum calcium level between PTH-treated and calcitriol/placebo-treated subjects was 0.349 (95 % CI = −0.383–1.082, p = 0.350) for PTH (1–34) and 0.414 (95 % CI = −0.238–1.066, p = 0.214) for PTH (1–84), indicating no significant increase in serum calcium level in the PTH-treatment groups relative to the calcitriol/placebo (control) group (Fig. 2a). In contrast, the 24-h urine calcium levels significantly decreased in the PTH (1–34)-treated group compared with the control group (standardized difference in means = −0.696, 95 % CI = −1.225 to −0.167, p = 0.010) (Fig. 2b).

No change in urine calcium level relative to control was observed in the PTH (1–84)-treatment group. PTH (1–34) therapy did not change serum phosphate levels compared with control (p = 0.053), but PTH (1–84) treatment resulted in a significant decrease in phosphate levels compared with control (standardized difference in means = −0.592, 95 % CI = −0.890 to −0.294, p = 0.000) (Fig. 2c).

Analysis of the data indicated heterogeneity among the studies for the serum levels of 1,25-dihydroxyvitamin D [Q = 11.18, p = 0.001, I² = 91.1 % for PTH (1–34); Q = 6.94, p = 0.008, I² = 85.6 % for PTH (1–84)]; and in 25-dihydroxyvitamin D levels for PTH (1–34) [Q = 4.35, p = 0.037, I² = 77.0 %]; therefore, a random effects model was used to generate the pooled estimates (Fig. 3a, b). The subgroup of PTH (1–84) indicated no heterogeneity among the studies for 25-dihydroxyvitamin D level (Q = 0.24, p = 0.623, I² = 0 %); therefore, a fixed-effects model was used to generate the pooled estimates (Fig. 3b).

The results showed that there was no difference in 1,25-dihydroxyvitamin D levels between PTH-replacement and calcitriol/placebo treatment groups regardless of types of PTH agent used (PTH (1–34): pooled standardized difference in means = 1.060, 95 % CI = −0.228–2.547, p = 0.163; PTH (1–84): pooled standardized difference in means = 0.26, 95 % CI = −0.912–1.565, p = 0.606) (Fig. 3a).

However, both PTH (1–34) (standardized difference in means = −0.954, 95 % CI = −1.863 to −0.044, p = 0.040) and PTH (1–84) (standardized difference in means = −0.639, 95 % CI = −1.207 to −0.071, p = 0.028) treatments were associated with a significant decrease in serum 25-dihydroxyvitamin D levels (Fig. 3b).

Sensitivity analysis, in which each study was left out in turn, indicated that the study of Winer et al. (2003) [18] had a mild influence over the pooled estimates for serum calcium levels (standardized difference in means = 0.493, 95 % CI = 0.003–0.983,
p = 0.049); pooled results became significant when Winer et al. (2003) [18] was removed (Fig. 4a). In addition, the study of Mannstadt et al. (2013) [13] may have overly impacted the result of the 24-h urine calcium level (standardized difference in means = −0.696, 95% CI = −1.225 to −0.167, p = 0.010); pooled results became statistically significant when Mannstadt et al. (2013) [13] was removed (Fig. 4b).

To assess whether the age of patients may have influenced our pooled results for the treatment of PTH (1–34) on both primary outcomes, subgroup analyses that evaluated the adult patient results were conducted (Fig. 5). Two studies with adult patients for each PTH (1–34) treatment were included in the analysis. The results showed that there was no association between serum calcium level and treatment of PTH (1–34) (standardized difference in means = 0.518, 95% CI = −0.795–1.831, p = 0.440). On the other hand, a significantly decrease in urine calcium level was found the PTH (1–34)-treated group compared with the control group (standardized difference in means = −0.803, 95% CI = −1.399 to −0.208, p = 0.008) (Fig. 5).
Quality assessment

Quality assessment indicated that all the studies were of good quality. All 4 of the studies were randomized controlled studies minimizing selection bias. There was low risk of attrition or reporting bias, and for the studies reported the necessary information, there was low risk of performance or detection bias. Three of the 5 studies had intention-to-treat analysis.

Discussion

The purpose of this study was to evaluate the efficacy of human PTH-replacement therapy in adults and children with hypoparathyroidism. This meta-analysis found PTH-replacement therapy, regardless if it was with PTH (1–34) or PTH (1–84), was not associated with a greater increase in levels of serum calcium compared with placebo/calcitriol control. The analysis also found that PTH (1–34) resulted in a significant decrease in urine calcium levels relative to placebo/calcitriol (p = 0.01), but there was no significant difference with regard to phosphorous compared with placebo/calcitriol control (p = 0.053). Serum phosphorus levels in children are normally higher compared with adult levels. In the study designed for children with chronic hypoparathyroidism, serum phosphorus was consistently above normal in both treatment groups [16]. PTH (1–84) treatment resulted in no change in urine calcium relative to placebo/calcitriol control (p = 0.689), but there was a significant decrease in serum phosphate levels (p < 0.001). There was no difference between either type of PTH therapy and placebo/calcitriol (p ≥ 0.163) Both PTH (1–34) and PTH (1–84) caused a significant decrease in serum 25-dihydroxyvitamin D levels (p ≤ 0.04) but not in 1,25-dihyrdroxyvitamin D. The differences in findings between the 2 therapies may reflect differences in the study designs or possible differences in biological activity between the molecules. We also performed subgroup analysis that evaluated only adults which found that in adults PTH (1–34) therapy did not result in a significant difference in serum calcium levels compared with placebo/calcitriol control (p = 0.440) but did significantly reduce urine calcium levels (p = 0.008). These findings are similar to those of the entire populations. The importance of
this meta-analysis study is that by evaluating the pooled data for PTH (1–34) and PTH (1–84) treatments, it gives additional insight into the benefit and the activity of the different PTH therapies in treating hypoparathyroidism.

Analysis of the efficacy of PTH (1–34) and PTH (1–84) separately found that mean serum calcium was maintained within or slightly below normal range (nonsignificant difference) but urine calcium was significantly decreased after the PTH (1–34) treatment. PTH (1–34) did reduce the urine calcium level to the normal range (1.25–6.25 mmol/24h). These findings may suggest that PTH (1–34) maintains the serum calcium level by increasing renal calcium reabsorption and decreasing urine calcium excretion.

In the RCTs included in this study, patients received oral calcium and vitamin D analogue(s) as supplement treatment. However, as above mentioned, short- and long-term complications indicate that large swings in serum calcium levels (hyper- or hypocalcemia) may occur after the treatment. Furthermore, studies with PTH (1–84) did not achieve this important goal of reducing urine calcium possibly because patients received large, fixed, single daily doses. Mean serum 1,25-dihydroxyvitamin D concentrations were maintained in the normal range but mean serum concentration of 25-hydroxyvitamin D decreased in both PTH (1–34) and PTH (1–84) groups. A decrease in serum level of 25-hydroxyvitamin D implied that PTH therapy maintained the serum level of 1,25-dihydroxyvitamin D by improving conversion of 25(OH)D by 1α-hydroxylase to 1,25(OH)2D. In an RCT reported by Mannstadt et al. (2013) [13], 1,25-dihydroxyvitamin D concentrations patients treated with PTH (1–84) were maintained in the normal range despite reductions in oral calcium and active vitamin D [13].

Potential advantages of PTH-replacement therapy is that it may result in improved maintenance of serum calcium levels and reduce the need for treating with calcium and active vitamin D or vitamin D analogues [6]. PTH-replacement therapy may also lower urinary calcium, improve bone quality, reduce ectopic tissue calcification, and improved quality of life [23, 24]. In addition, there is evidence that hypoparathyroidism is associated with elevated cholesterol levels, a risk factor for cardiovascular disease [25]. It is unclear if PTH-replacement therapy would affect cholesterol levels.

This meta-analysis suggests that PTH-replacement therapy can simultaneously maintain normal serum and urine calcium. Several prior studies found PTH-replacement therapy reduced the need for additional calcium or vitamin D and improved bone mineral density [14]. We did not analyze if the use of PTH-replacement therapy resulted in a reduction in the need for calcium supplementation or vitamin D or its analogues. We also did not evaluate the impact of PTH-replacement therapy on bone mineral density.

Currently, PTH is marketed for the treatment of osteoporosis and is only available at a fixed dose of 20μg (teriparatide; Forteo®, Eli Lilly and Company, Indianapolis, IN, USA) [28]. PTH (1–84) is available in the U.S. at a once daily dosage of 50μg (Natpara®, NPS Pharmaceuticals, Inc, Bedminster, NJ, USA) [26]. However, due to the occurrence of osteosarcomas and death in rat toxicology studies of rhPTH (1–34) [27], the FDA does not permit administration of PTH (1–34) to children or adults younger than 24 years of age, and PTH is not approved by the FDA for use in hypoparathyroidism [12, 27]. PTH (1–84) was only recently approved in 2015 in the US for the treatment of osteoporosis and because of the potential risk of osteosarcoma, it is recommended only for patients who cannot be well-controlled on calcium supplements and active forms of vitamin D alone. The available preparations of PTH can only be used once daily, as twice daily administration will cause hypercalcemia in most patients [26, 28].

PTH-replacement therapy may work best using flexible dosing to adjust to the needs of different patients [13]. One study evaluated the efficacy and safety of PTH (1–34) in adults with hypoparathyroidism who received titrated PTH dosing aimed at normalizing calcium levels in the blood and urine [13]. In the study, the doses of the PTH (1–34) or calcitriol were adjusted to achieve serum calcium levels within the normal, or just below the normal, range [13]. The study found that, during a 3-year follow-up, serum calcium levels and urine calcium excretion were essentially within the normal range in the PTH (1–34) treated patients [20]. In contrast, only the serum calcium levels were within the normal range for the calcitriol treated patients. The bone mineral content and bone mineral density also improved to a greater extent with the PTH (1–34) compared with the calcitriol treatment [13]. In general, the findings were similar to the study of Winer et al. (2010) [16] that also used flexible dosing in children aged 5–14 years except there was no difference in the serum calcium levels between PTH (1–34) and calcitriol [16]. In contrast to PTH (1–34), studies with PTH (1–84) have only assessed fixed doses of PTH. Currently due to the fixed daily dosing of commercially available PTH-replacement therapy, the use of these drugs should be as an experimental treatment in patients in which calcium levels cannot be maintained using conventional methods [6]. Further, well designed studies that use similar dosing strategies are required to better understand the long-term efficacy and safety of treating hypoparathyroidism with PTH-replacement therapy.

All included studies were randomized trials (4 being RCTs and one being a randomized cross-over study). However, our meta-analysis has several limitations. The overall sample size was small, partly reflecting the rarity of this disease. The studies differed in populations (3 enrolled primarily female adults women, and 2 studies were performed in children) and active drug (2 studies PTH (1–84) and 3 investigated PTH (1–34). Although, the pharmacokinetics and pharmacodynamics may differ slightly between PTH (1–84) and PTH (1–34) [26, 28], the published results do not indicate any apparent difference in efficacy between the 2 molecules [6, 23]. However to date, there has not been a head-to-head study between PTH (1–84) and PTH (1–34) [6]. In addition, the studies with PTH (1–34) and PTH (1–84) differed in design and purpose; PTH (1–34) studies titrated doses of the molecule to normalize both urine and calcium levels, while studies with PTH (1–84) used a fixed dose along with calcitriol and calcium. Calcitriol, which was co-administered with PTH in 3 of the 5 included studies has potent calcemic and calcuic effects, which may confound the interpretation of the “true” PTH effect. Another limitation of our analysis is that it did not evaluate changes in symptoms resulting from PTH-replacement therapy. The follow-up time in the 3 of the 4 the studies, which enrolled adults, was <6 months [13, 14, 21]. The other study evaluated PTH (1–34) therapy up to 3 years in adults and found it was safe and effective [18]. Additional long-term studies are necessary to further determine the long-term effects of PTH therapy. This is important as treatment of hypoparathyroidism, a life-long disorder, requires long-term therapy [6]. Only one study investigated the twice daily administration of PTH-replacement therapy in children (5–14 years of age) [16]. They found that, up to 3-years, treatment with PTH (1–34) was well
tolerated and was similar to calcitriol treatment in maintaining normal serum and urine calcium levels, kidney function, bone mineral accrual, and developmental growth. Similar to adults, longer term studies in children are required to establish the efficacy and safety of PTH-replacement in treating hypoparathyroidism in this young patient population. In addition, there is evidence that hyperparathyroidism may be associated with thyroid carcinomas in about 3% of patients [29]. It would be of interest to further investigate the relationship of hyperparathyroidism and the risk of thyroid cancer and the effect of PTH therapy on this risk.

Conclusion

In conclusion, our meta-analysis suggests that, in patients with hypoparathyroidism, PTH (1–34), but no PTH (1–84) replacement therapy, can maintain the serum calcium levels in normal range by reducing the levels of urine calcium. However, serum phosphate level is reduced by PTH (1–84)-replacement therapy but not by PTH (1–34). Both PTH (1–34) and PTH (1–84)-replacement therapy may maintain the serum level of 1,25-dihydroxyvitamin D. It may be achieved by improving conversion of 25-dihydroxyvitamin D by 1α-hydroxylase to 1,25-dihydroxyvitamin D, which results in a decrease in serum levels of 25-dihydroxyvitamin D.

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Conflict of Interest

The authors declare no conflict of interest.

References