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The effects of adequate dietary calcium intake in patients with hypoparathyroidism non-adherent to treatment: a prospective randomized controlled trial

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SUMMARY

OBJECTIVE: A significant problem that compels clinicians in the conventional treatment of hypoparathyroidism is patients' non-adherence to treatment. This study aimed to evaluate the effects of adequate Ca intake with dietary recommendations among hypoparathyroidism patients who persistently use Ca supplementation irregularly on plasma Ca and phosphate levels.

METHODS: This prospective, randomized, controlled study was conducted on patients diagnosed with chronic hypoparathyroidism who persistently interrupt Ca supplementation therapy and therefore have a hypocalcemic course. Patients with a total daily Ca intake below 800 mg were randomized. All patients were advised to keep the doses of active vitamin D and Ca supplements they were currently using. The patients in the study group (n=32) were advised to consume 1,000–1,200 mg of Ca daily, and the patients in the control group (n=35) were advised to continue their diet according to their daily habits. After 12 weeks of follow-up, the patients' laboratory values were compared between groups to assess treatment goals.

RESULTS: The mean of the total Ca level was 8.56±0.36 mg/dL in the study group and was found to be significantly higher than that in the control group, which was 7.67±0.48 mg/dL ($p<0.001$). The mean serum phosphate and serum Ca-P product levels were significantly higher in the study group ($p<0.001$) but did not exceed the safe upper limits in any patient.

CONCLUSION: A suitable increase in dietary Ca intake could effectively control hypocalcemia in patients with hypoparathyroidism who persistently interrupt the recommended calcium supplementation.

KEYWORDS: Hypoparathyroidism. Dietary calcium. Medication non-adherence.

INTRODUCTION

Hypoparathyroidism (hypoPT) is a mineral metabolism disease characterized by hypocalcemia due to an insufficiency or absence of parathormone (PTH) synthesis[1]. The primary goals of hypoPT treatment are to correct hypocalcemia and prevent disease-related complications[2]. The hypoPT management guidelines recommend conventional therapy as the first-line therapy in hypoPT treatment[2]. Most diseases that develop due to hormone deficiency are usually treated by replacing the missing hormone. However, PTH replacement therapy is recommended for individuals who cannot be adequately controlled using conventional hypoPT therapy[3]. Moreover, it cannot be used widely due to its high cost and lack of long-term safety data[4]. Therefore, most hypoPT patients are treated with the conventional approach.

Oral Ca salts and active vitamin D supplements form the basis of conventional treatment[5]. However, this approach does not always provide adequate or consistent control of the biochemical and clinical aspects of the disease. Adverse short-term and long-term complications include large fluctuations in serum Ca concentrations and risks of calcifications in tissues[6]. Further critical problems that compel clinicians in daily practice related to conventional hypoPT treatment are patients' non-compliance with treatment and irregular use of oral Ca and active vitamin D supplements despite persistent information and warnings[7]. As a result, patients who cannot achieve their treatment goals are frequently encountered. In this patient group, when PTH replacement, which can be an alternative approach, cannot be provided, serious difficulties are experienced in treating this condition.

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The recommended daily Ca intake for hypoPT patients is the same as in the general population[8,9]. In this study, we aimed to examine the effects of adequate Ca intake with dietary recommendations among hypoPT patients who persistently use Ca supplementation therapy irregularly and therefore have low plasma Ca and P levels.

METHODS

Ethical standards

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of the University of Health Sciences, Şişli Hamidiye Etfal Training and Research Hospital (Date 28.12.2021/No. 1973). Informed consent was obtained from all individual participants included in the study.

Design and study population

This prospective, randomized, controlled clinical study was conducted with patients who applied to the Endocrinology outpatient clinic in 2022 and received conventional treatment for hypoPT. Patients who came for regular follow-ups at least twice a year, who regularly took the recommended active vitamin D treatment but persistently never or incompletely used Ca supplementation, and whose albumin-corrected plasma total Ca levels were consistently 8 mg/dL and below were identified. Patients who skipped Ca supplementation regularly, at least thrice a week, were defined as non-adherent to Ca supplementation therapy. Patients with chronic kidney disease, a history of urolithiasis, high 24-h urinary Ca excretion (>300 mg/day for males, >250 mg/day for females), serum Ca-P product levels>55 mg^2/dL^2, plasma magnesium (Mg) levels outside the normal reference range, any diagnosed gastrointestinal disease that may affect oral drug or nutrient absorption, and neuropsychiatric disorders that would prevent them from making a food follow-up chart were excluded from the study.

A dietitian contacted the patients for the second screening and informed them of the amounts of Ca in each portion. The patients were trained in preparing a food-tracking chart and asked to keep records for 2 weeks. Patients who did not complete their nutritional follow-up chart, who did not come for control, or whose average daily Ca intake (diet and supplementation) was 800 mg/day and above were excluded from the study.

For randomization, patients were numbered according to their admission order for 2022. Those with odd numbers were classified as the study group, and those with even numbers were classified as the control group. Finally, patients were given nutritional follow-up chart forms and advised not to change their active vitamin D and Ca supplement doses and to keep daily records for 12 weeks. The patients in the control group were advised to continue to eat according to their daily habits. The patients in the study group were advised to consume 1,000–1,200 mg of Ca daily. Furthermore, they were warned that their total daily Ca intake should stay within 800 mg and not exceed 1,500 mg. After 12 weeks, patients in the study group with an average daily Ca consumption below 800 mg and those in the control group with an average daily Ca consumption of 800 mg and above were excluded from the evaluation (Figure 1).

The primary endpoint was the proportion of patients at Week 12 who achieved plasma total Ca levels in the lower limit of or slightly below the normal range (the target range of 8–9.5 mg/dL). The secondary endpoint was that the 24-h urinary Ca excretion, plasma P, and serum Ca-P product levels did not exceed the treatment targets recommended by the hypoPT treatment guidelines. The serum Ca-P product levels were calculated by multiplying plasma calcium and phosphate levels.

Statistical analysis

The conformity of the data to the normal distribution was evaluated using the Shapiro-Wilk test. Mean and standard deviations were used for normally distributed variables. Medians and ranges were used for non-normally distributed variables. Chi-square (χ^2) and Fisher's exact tests were used to compare categorical data. Student's t-test and Mann-Whitney U test were used to compare parametric and nonparametric data, respectively, between the study and control groups. Statistical significance levels were accepted as $p<0.05$.

RESULTS

Overall, 216 patients were screened, and 72 were randomly assigned into two. Notably, 32 patients from the study group and 35 from the control group completed the study (Figure 1). The patients' baseline characteristics, demographic information, and laboratory values were similar between the study and control groups (Table 1).

While the mean prescribed Ca intake per day at baseline was similar between the groups, the dietary and associated total Ca intake were higher in the control group (p-value=0.046 and 0.026, respectively) than in the study group.

Compliance with the dietary recommendations was excellent in the study group (34/36, 94.4%). The data of both groups after 12 weeks of follow-up are shown in Table 1.

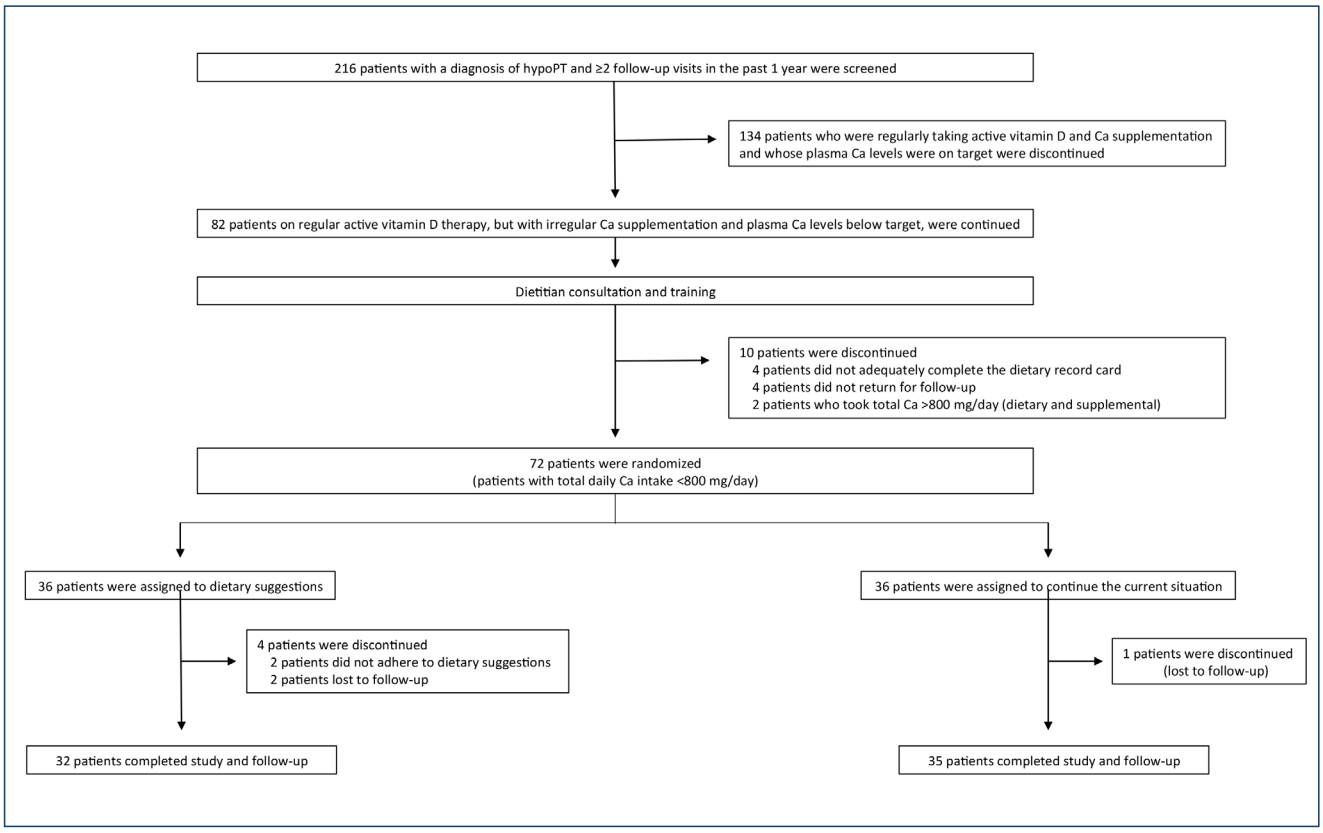

Figure 1. Study protocol.

The mean dietary Ca intake and total daily Ca intake were statistically significantly higher in the study group than in the control group (p<0.001). The mean Ca levels, which was the primary endpoint of the study, was 8.56±0.36 (7.58–9.13) mg/dL in the study group and was significantly higher than that in the control group, which was 7.67±0.48 (6.76–8.78) mg/dL (p<0.001). Furthermore, 87% of patients in the study group attained the target range of serum Ca levels (8–9.5 mg/dL), and the remaining 13% attained very close values (the least was 7.7 mg/dL). In the control group, 3 (8.5%) of the 35 patients attained the target range.

During the follow-up period, no patients in the study group described paresthesia symptoms. The value of mean Ca excretion in 24-h urine in the study group was higher than that of the control group (p<0.001). However, no patient exceeded 250 and 300 mg/day for women and men, respectively. The mean serum P and serum Ca-P product levels were significantly higher in the study group (p<0.001) than in the control group. For the serum P levels, no patient exceeded the upper limit of the reference range (2.5–4.5 mg/dL) by more than 1 mg/dL, and the serum Ca-P product levels did not exceed the safe upper limit of 55 mg^2/dL^2 in any patient.

When the GFR values were compared with the MDRD formulation, it was found to be 98.9 in the study group and 103.3 in the control group (p=0.035). During the follow-ups, nephrocalcinosis, nephrolithiasis, and extraskeletal complications were not observed in the patients.

Table 2 compares the study group values before and after the dietary intervention during the 12-week follow-up period.

Serum Ca levels increased from 7.29 to 8.56, serum P levels increased from 4.43 to 5.21, 24-h urinary Ca excretion increased from 146.5 to 229.6, and serum Ca-P product values increased from 32.35 to 44.59 after dietary changes (p<0.001). Additionally, increased serum creatinine levels (0.75–0.79) and decreased GFR levels (100.9–89.9) were detected.

DISCUSSION

In this observational controlled study, we provide information on the effect and safety of adequate dietary Ca intake in correcting hypocalcemia in hypoPT patients who are incompatible with Ca supplementation and have a hypocalcemic course. Most (87.5%) patients with adequate dietary Ca intake reached the primary endpoint, the target Ca level, compared with only 7.7% in the control group.

Table 1. Patients' baseline and after 12 weeks of follow-up characteristics.

	Study (n=32)	Control (n=35)	p-value *
Baseline characteristics			
Age, years	52.3±8.8 (29–64)	51.2±9.5 (28–64)	0.744
Gender			
°Women	20 (62.5%)	23 (65.7%)	
°Men	12 (37.5%)	12 (34.3%)	0.784
Duration of hypoPT, years			
°≤5 years	2 (6.3%)	2 (5.7%)	
°5–10 years	12 (37.5%)	14 (40%)	
°≥10 years	18 (56.2%)	19 (54.3%)	0.976
Cause of hypoPT			
°Idiopathic, autoimmune disease	10 (31.2%)	12 (34.3%)	
°Post-surgical disease	22 (68.8%)	23 (65.7%)	0.791
Prescribed calcitriol dose, µg/day			
°0.25–0.50	20 (62.5%)	23 (65.7%)	
°>0.50	12 (37.5%)	12 (34.3%)	0.784
Mean prescribed calcitriol dose, µg/day	0.664±0.274	0.650±0.265	0.848
Mean Ca intake, mg/day			
°Prescribed	131.3±252.0 (0–600)	137.1±255.6 (0–600)	0.924
°Dietary	375.8±146.1 (150–750)	475.0±208.1 (150–800)	**0.046**
°Total	504.7±190.3 (250–800)	612.1±165.8 (275–800)	**0.026**
Albumin-corrected total serum Ca (mg/dL)	7.29±0.22 (6.88–7.59)	7.28± 0.31 (6.29–7.59)	0.66
Serum phosphate (mg/dL)	4.43±0.41 (3.48–4.98)	4.58±0.44 (3.68–5.39)	0.14
Serum magnesium (mg/dL)	1.75± 0.12 (1.56–1.97)	1.76±0.13 (1.51–1.96)	0.83
Serum 25 (OH) vitamin D (ng/mL)	19.99±6.56 (5.7–37.1)	18.98±6.55 (6.4–34.9)	0.53
Serum creatinine (mg/dL)	0.75±0.12 (0.43–0.95)	0.74±0.11 (0.50–1.02)	0.71
GFR (mL/min/1.73 m²)	100.97±7.16 (90–115)	102.9±9.66 (90–126)	0.60
Serum Ca-P product (mg²/dL²)	32.35±3.60 (24.3–37.7)	34.07±3.79 (25.3–40.4)	0.06
Urine Ca, mg/24 h	146.5±35.9 (89.3–206.1)	136.3±38.7 (47.5–193.6)	0.27
Data after 12 weeks of follow-up			
Mean Ca intake, mg/day			
°Prescribed	131.3±252.0 (0–600)	137.1±255.6 (0–600)	0.924
°Dietary	1,050.0±179.6 (450–1,350)	510.0±232.3 (150–800)	**<0.001**
°Total	1,185.9±167.8 (1,000–1,650)	647.1±162.7 (300–800)	**<0.001**
Albumin-corrected total serum Ca (mg/dL)	8.56±0.36 (7.58–9.13)	7.67±0.48 (6.76–8.78)	**<0.001**
Number of patients who reached the target Ca value (8–9.5 mg/dL)	28 (87.5%)	3 (8.5%)	
Number of patients with hypocalcemia requiring emergency admission	0	0	
Number of patients with hypocalcemia requiring emergency admission	0	9 (25.7%)	
Urine Ca, mg/24 h	229.6±40.1 (133.6–296.2)	163.1±38.5 (96.3–245.2)	**<0.001**
Serum phosphate (mg/dL)	5.21±0.39 (4.38–5.88)	4.94±0.41 (4.25–5.79)	**0.01**
Serum Ca-P product (mg²/dL²)	44.59±3.97 (36.3–51.5)	34.6±4.9 (28.1–50.8)	**<0.001**
Serum creatinine (mg/dL)	0.79±0.11 (0.57–1.01)	0.74±0.11 (0.50–1.02)	0.11
GFR (mL/min/1.73 m²)	98.9±8.7 (84–114)	103.3±7.9 (87–128)	**0.035**

*Significance level: 0.05. Statistically significant values are indicated in bold.

Table 2. Comparison of the study group values before and after dietary changes.

	Before dietary changes	After dietary changes	p-value*
Mean Ca intake, mg/day			
°Prescribed	131.3±252.0 (0–600)	131.3±252.0 (0–600)	1
°Dietary	375.8±146.1 (150–750)	1,050.0±179.6 (450–1,350)	**<0.001**
°Total	504.7±190.3 (250–800)	1,185.9±167.8 (1,000–1,650)	**<0.001**
Albumin-corrected total serum Ca (mg/dL)	7.29±0.22 (6.88–7.59)	8.56±0.36 (7.58–9.13)	**<0.001**
Serum phosphate (mg/dL)	4.43±0.41 (3.48–4.98)	5.21±0.39 (4.38–5.88)	**<0.001**
Serum creatinine (mg/dL)	0.75±0.12 (0.43–0.95)	0.79±0.11 (0.57–1.01)	**0.001**
GFR (mL/min/1.73 m^2)	100.97±7.16 (90–115)	98.9±8.7 (84–114)	**0.009**
Serum Ca-P product (mg^2/dL^2)	32.35±3.60 (24.3–37.7)	44.59±3.97 (36.3–51.5)	**<0.001**
Urine Ca, mg/24 h	146.5±35.9 (89.3–206.1)	229.6±40.1 (89.3–206.1)	**<0.001**

*Significance level: 0.05. Statistically significant values are indicated in bold.

We observed that all 216 patients diagnosed with hypoPT screened for our study used Ca-gluconate and active vitamin D supplements, so they received conventional treatment. Therefore, the hypoPT treatment guidelines recommend conventional therapy as the first-line therapy for hypoPTH, although new treatment options are available[3,8,10,11]. Conventional treatment is primarily intended to correct hypocalcemia, not as a physiological replacement therapy for PTH deficiency. Therefore, PTH analogs or the administration of recombinant human PTH is recommended for patients unable to achieve treatment goals with conventional therapy[12,13]. PTH analogs limit the need for Ca supplements that are not well tolerated, especially when high doses are required[14]. However, the cost of PTH replacement therapy is considerably higher than that of conventional therapy. In addition, long-term safety data are insufficient, thus limiting its use as a standard replacement therapy for all hypoPT patients[4]. We found that only one of the patients screened within the scope of our study was started on teriparatide (PTH 1-34) treatment 3 years ago. However, after 3 months of use, it was discontinued due to the high cost, and conventional treatment was resumed.

It is nearly impossible to manage hypoPT by ensuring adequate Ca intake through diet alone. Therefore, Ca supplements are necessary. Typically, patients reportedly require 1–2 g of additional Ca, given in divided doses of 500 mg at a time[15,16]. One common problem in daily practice related to conventional treatment is patients' non-compliance. We found that 82 (37.9%) of the 216 patients screened for our study did not use Ca supplementation regularly as recommended. The hypoPT treatment guidelines emphasize the significance of this problem. Reportedly, the numerous pills required daily and the gastrointestinal side effects of Ca preparations contribute to the incompatibility[17]. Unfortunately, the number of studies evaluating drug compliance and related factors in hypoPT patients is limited in the literature. In a study, the rate of non-compliance with $CaCO_3$ treatment was 51.7%, and the rate of non-compliance with calcitriol treatment was 28.3%[7]. Studies on patient compliance with Ca supplementation were mainly conducted in patients diagnosed with osteoporosis. In a study in which 7,624 patients who have prescribed Ca and vitamin D treatment were examined, it was observed that 27.7% of the patients did not continue their Ca supplementary treatment 1 year after starting[18].

Controlling hypocalcemia by providing adequate dietary Ca without Ca supplementation is challenging. A study conducted on subjects without diseases related to Ca metabolism showed a significant correlation between the change in dietary Ca intake and plasma and urinary Ca levels[19]. In addition, dairy products, the primary source of Ca in the diet, are rich in phosphate[20]. Hence, there is concern that overconsumption of dairy products for Ca supplementation may also increase P, thus increasing serum Ca-P product. In the hypoPT treatment guidelines, the recommended dietary Ca intake in hypoPT patients is the same as that recommended for the general population[15]. The daily Ca consumption recommended by the Institute of Medicine for healthy individuals has been accepted by many scientific communities, such as the National Osteoporosis Foundation, and is recommended in exact amounts. According to this recommendation, 1,000 mg/day Ca consumption is recommended for those aged 19–50 years, and 1,200 mg/day Ca consumption is recommended for those aged 50 and above. Ca intake exceeding 1,200–1,500 mg may increase the risk of kidney stones, cardiovascular events, and stroke[9,21].

Managing hypoPT patients who are undergoing conventional treatment but hinder the recommended treatment and therefore develop a hypocalcemic course and cannot be

switched to alternative options due to cost is severely challenging. To date, no study has examined the effects of increasing the amount of Ca in the daily diet of hypoPT patients in a controlled manner. When we examined the daily Ca consumption of the patients who were screened for the study and asked to prepare a nutritional follow-up chart, we observed that their daily Ca intake was well below that of a healthy adult. Daily Ca consumption was 375 mg/day in the study group and 475 mg/day in the control group. In a study, the average Ca intake in adults aged 51 years and older was 674 mg/day, which was significantly less than the adequate daily intake of 1,200 mg[22]. After the patients in the study group were advised to take Ca in the amount recommended by the treatment guidelines[9], it was observed that daily dietary Ca consumption increased from 375 (150–750) mg/day to 1,050 (450–1,350) mg/day and total daily Ca intake increased from 504 (250–800) mg/day to 1,185 (1,000–1,650) mg/day. However, the prescribed Ca amounts for the patients did not change.

Limitations

It is known that the effects of dietary Ca changes on plasma Ca and P levels and urinary Ca excretion occur within a short time, even daily. However, the study period may not be sufficient to achieve the hypoPT treatment goals of these changes and evaluate the safety of complications, such as nephrocalcinosis and nephrolithiasis. Another limitation of the study is that the upper limit of the recommended dietary Ca amount (1,500 mg/day) was not exceeded by any of the patients included in the study; thus, the warnings and the laboratory and clinical implications of exceeding this amount could not be tested.

CONCLUSION

This is the first prospective randomized controlled study to examine the effect of adequate dietary Ca intake in correcting hypocalcemia in patients with hypoPT who are incompatible with Ca supplementation therapy. The recommendation to consume only the amount of Ca a healthy adult should take makes the proposed approach immediately applicable. The results show that a steady increase in dietary Ca intake effectively controls hypocalcemia. Although plasma P and serum Ca-P product increased, they did not exceed the safe upper limit. Additionally, we observed that they did not cause complications during the study by deviating from the treatment targets of hypoPT. Furthermore, patients' compliance was high, and they tolerated the increased Ca consumption well.

AUTHORS' CONTRIBUTIONS

MMC: Investigation, Methodology, Project administration, Writing – original draft. **AB:** Conceptualization, Investigation, Writing – review & editing. **ÇD:** Data curation, Resources. **HK:** Data curation, Visualization. **YA:** Supervision, Validation. **MK:** Formal Analysis, Software. **ZMYK:** Resources. **FYÖ:** Methodology.

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