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ORIGINAL ARTICLE

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The prevalence and natural history of normocalcaemic hypoparathyroidism in a United Kingdom referral population

Marian Schini[1] | Rebecca Stirling[1] | Richard M. Jacques[2] | Eleanor Oakes[3] | Nicola F. A. Peel[3] | Jennifer S. Walsh[1] | Richard Eastell[1]

[1]Department of Oncology and Metabolism, University of Sheffield, Sheffield, UK

[2]School of Health and Related Research (ScHARR), University of Sheffield, Sheffield, UK

[3]Sheffield Teaching Hospitals National Health Service Foundation Trust (STH NHS FT), Sheffield, UK

Correspondence
Marian Schini, Department of Oncology and Metabolism, University of Sheffield, Sheffield, UK.
Email: m.schini@sheffield.ac.uk

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Abstract

Context: Normocalcaemic hypoparathyroidism (NHYPO) is characterized by low levels of parathyroid hormone (PTH) with normal levels of calcium. There is little in the current literature on this disease, with only two studies published on its prevalence, while its natural history remains relatively unknown.

Objectives: To identify the prevalence of NHYPO in a UK referral population and to study the natural history of the disorder.

Design: Retrospective study. Five-year follow-up.

Patients: 6280 patients referred for a BMD measurement in a Metabolic Bone referral centre.

Measurements: Prevalence of NHYPO and variability of calcium.

Results: Based on laboratory results on the index day, 22 patients with NHYPO were identified. Four patients were excluded due to non-PTH-induced hypocalcaemia and unconfirmed data. The final prevalence was 0.29%. Only 67% had persistent normocalcaemia, and the rest had intermittent hypocalcaemia. Two of these patients also had persistently low PTH on two occasions. Most of the patients had one PTH measurement available. No patient developed permanent hypoparathyroidism.

Conclusions: The prevalence calculated from this UK referral population is lower when compared to results from previous studies. NHYPO patients often have episodes of hypocalcaemia with some cases having no apparent reason for calcium levels below the reference range.

KEYWORDS

calcium, calcium metabolism disorders, epidemiology, hypocalcaemia, hypoparathyroidism, parathyroid diseases, parathyroid gland, prevalence

1 | INTRODUCTION

Calcium is an important mineral in the human body; its regulation within tight normal limits is of great importance. Parathyroid hormone (PTH) is the main regulator of calcium homeostasis, and it regulates calcium levels by altering bone resorption, renal calcium excretion and the production of $1,25(OH)_2D$.[1]

Endocrine disorders are often characterized by a clinical and a subclinical form, such as subclinical hyperthyroidism, characterized by suppressed TSH with normal thyroid hormone levels.[2] Following

a similar pattern, a new phenotype of PHPT has been presented recently in the literature. Normocalcaemic hyperparathyroidism is a disorder of calcium metabolism which is characterized by persistently normal calcium levels and consistently elevated PTH values after other causes of secondary hyperparathyroidism are excluded.[3]

On the other side of the spectrum of calcium-related disorders, hypoparathyroidism is a rare disorder, characterized by low levels of calcium due to a low PTH secretion. The most common cause is acquired hypoparathyroidism, mainly seen after anterior neck surgery. A pathophysiological counterpart to normocalcaemic hyperparathyroidism is normocalcaemic hypoparathyroidism (NHYPO), which is characterized by normal levels of calcium with low levels of parathyroid hormone (PTH). To our knowledge, there is currently no official definition for this disorder. There is little in the current literature, with only two studies published on its prevalence, while its natural history remains relatively unknown.[4,5] The prevalence in these studies is reported to be 1.1%-2.4% at baseline. Two of these three populations, which were quite different, [women from five European cities for the Osteoporosis and Ultrasound Study (OPUS) and participants of the Dallas Heart Study (DHS), a population-based cohort for the evaluation of cardiovascular disease] were then checked 6 and 8 years later (1416 and 2122 patients, respectively, from each study went into follow-up), and only 1.1% (out of the original 57 patients, 35 had blood measurements and only 15 had persistent findings) and 0.09% (out of the 68 patients identified, 26 had a follow-up and 2 had persistent findings), respectively, were still characterized as having NHYPO. None developed hypoparathyroidism. Serum calcium and PTH were only checked on two occasions in these studies, so the natural history of serum calcium is unclear. To our knowledge, no one has evaluated this before.

The primary aims of this study were to identify the prevalence of NHYPO and to study the natural history of the disorder, hypothesizing that individuals presenting as NHYPO may have more labile calcium than the general population. A second aim was to compare the variability of adjusted calcium between NHYPO patients and a control group from the same cohort.

2 | MATERIALS AND METHODS

2.1 | Study population

The work was performed at the Metabolic Bone Centre (MBC) at Sheffield Teaching Hospitals National Health Service Foundation Trust (STH NHS FT) in the United Kingdom. Data from patients referred for a bone mineral density (BMD) measurement between 14 January 2013 and 27 July 2017 were retrospectively evaluated. All the patients included in the analysis had a laboratory evaluation including calcium and PTH, performed within 28 days from their scan. In this department, a laboratory work-up for secondary osteoporosis is performed in patients having any of the following findings: low BMD for age (Z-score <−2.0), vertebral fracture and/or unexplained, accelerated bone loss since a previous scan. The day of the laboratory investigations was defined to be the index day. Any other results of calcium and PTH before and after the index day were retrieved from the hospital's records and were used to study the natural history of the disease. Although biochemical data were available from 2009 onwards, only the data after 14 January 2013 were used, because at that point the laboratory changed the assay for serum calcium, and this would probably affect the accuracy of the results. The end of the follow-up period was 31 July 2018.

The analysis did not require any ethical approval according to the Sheffield Teaching Hospitals Clinical Research Office; it falls under the 'case note review' category.

2.2 | Biochemical measurements

Blood was drawn at any point of the day, so patients were not fasting. All the samples were analysed in the Chemical Pathology Laboratory, Sheffield Teaching Hospitals NHS Foundation Trust. Serum calcium was measured using a Roche/Hitachi Cobas 8000 e702 automated clinical chemistry analyser (Roche Diagnostics GmbH, Mannheim, Germany). The interassay coefficient of variation as measured in the laboratory is 1.1%-1.5% at 1.52 mmol/L and 0.6%-1.1% at 3.07 mmol/L. Albumin measurement was performed using a Roche/Hitachi Cobas 8000 e702 analyser. The interassay coefficient of variation as measured by the laboratory is 1.5%-2.4% at 33.9 g/L and 1.0%-1.7% at 59.7 g/L. The albumin-adjusted calcium was used for this study and was calculated using the following equation (as used by the laboratory). The method by which the laboratory established its equation was based on a protocol published by Barth et al.[6]

$$\text{Adjusted Ca} = \text{Total Ca} + \left[0.0172\ (43 - \text{Albumin})\right]$$

The Pathology Harmony reference range has been in use for adjusted calcium in the UK since 2011; the range reported is 2.20-2.60 nmol/L (8.8-10.4 mg/dL).[7]

Intact PTH (second generation) was measured using an immunoassay method by the Roche Cobas 8000 e602. The interassay coefficient of variation (CV) measured in the laboratory is 2.2%-3.2% at 34 ng/L, 1.6%-1.7% at 94 ng/L and 1.4%-1.8% at 839 ng/L, while the reported reference range by the manufacturer was 15-65 ng/L (1.6 - 6.9 pmol/L).

25(OH)D was measured using a competitive binding protein assay and was performed by Roche modular analytics Cobas E170. The laboratory interassay coefficient of variation for this assay is 6.5%-9.9% at 48.2 nmol/L and 4.5%-6.3% at 92.3 nmol/L. Patients with a level greater or equal to 50 nmol/L were considered replete.[8]

Creatinine was measured using a Roche/Hitachi Cobas c8000 e702 analyser. The interassay coefficient of variation for this assay was 2.7%-6.1% at 55.7 μmol/L and 2.3%-4.0% at 458 μmol/L. The equation used to calculate eGFR was the Modification of Diet in Renal Disease (MDRD) Study equation. This equation changed in August 2015; the Chronic Kidney Disease Epidemiology Collaboration

(CKD-EPI) equation has been in use since then.[9] A level ≥60 mL/min/1.73m^2 was considered as normal.

Alkaline phosphatase was measured using a Roche/Hitachi Cobas c8000 e702 analyser. The interassay coefficient of variation for this assay was 2.4% at 92.8 IU/L and 1.7% at 224 IU/L. The reported reference range was 30-130 IU. The same analyser was used for the measurement of serum phosphate, and the interassay coefficient was 1.4% at 1.23 mmol/L and 1.2% at 2.04 mmol/L. The reported reference range was 0.8-1.5 mmol/L.

Bone mineral density was performed using dual-energy X-ray absorptiometry (DXA) of the lumbar spine and the proximal femur in posteroanterior projection. At the time of the study, there were three Hologic DXA scanners within the centre. The least significant change (LSC) used in the MBC was 4.5% for both the spine and the hip.

2.3 | Statistical analysis

Due to the fact that calcium and PTH are not independent variables, it was considered best to use a bivariate statistical approach to define the different categories of patients. Mahalanobis distance (MD) is a multidimensional generalization of the idea of measuring how many standard deviations (SD) away an observation is from the mean of a distribution. Observations are considered outliers if $MD^2 > X^2_{2;0.975} = 7.378$ [97,5th percentile of a chi-squared (X) distribution with two degrees of freedom].[10,11] The correlation analysis of adjusted calcium and PTH was performed based on a log10 transformation of the two variables. A similar approach has been used in the past to evaluate the prevalence of NHYPO in a different group of patients.[4] Using this method, subjects were identified as 'normal' if they were inside the ellipse and 'abnormal' if they were outside. Using the laboratory reference intervals for calcium and PTH, patients were divided into 10 categories as described below. 'High' or 'low' are referred to values of either adjusted calcium or PTH being above or below the reference range, respectively.

To compare the variability of calcium in the two groups, the within-subject standard deviation was calculated. The analysis of variance method was used to calculate the within-subject variance, as this method deals with the case of subjects having different numbers of observations. To follow this method, we first checked the assumption that the standard deviation was unrelated to the magnitude of the measurement. This was done graphically by plotting the individual subjects' standard deviations against their means and analytically by calculating a rank correlation coefficient.[12]

The independent-samples t test and the Mann-Whitney test were used to compare quantitative data, while chi-square was used for the analysis of categorical data. For the comparison of the overall measurements of PTH and adjusted calcium resulting from follow-up, we used a mixed linear model. Individual variability was modelled using a random effect, and the difference between groups was estimated using a fixed effect. The statistical analyses have been performed using the R Studio statistical software version 1.1.442 (RStudio, Inc, Boston).

2.4 | Definitions of the different groups

As mentioned in the Statistical analysis section, patients were divided into ten categories based on their laboratory intervals for adjusted calcium and PTH. The groups of interest for this study were defined as follows: normal: anyone inside the ellipse; provisional normocalcaemic hypoparathyroidism (NHYPO): normal adjusted calcium and low PTH on the index date; and hypoparathyroidism: low adjusted calcium and low PTH. In order to characterize these groups further, the following procedures were followed.

For the NHYPO group, the patients' medical notes were reviewed to look for other causes of the abnormalities found. Any unconfirmed data were excluded. For the control population, a random sample of 300 subjects from inside the ellipse having normal eGFR and being vitamin D replete (as defined above) on the index date was chosen.

3 | RESULTS

In total, 6293 patients attended the Metabolic Bone Centre and were assessed for secondary osteoporosis from January 2013 to July 2017. All these patients had a BMD measurement and a laboratory evaluation. Thirteen patients did not have PTH available on the index day and were excluded. The total number of patients analysed was 6280; their mean age was 66 years; and 72% were female. All these patients were given a study ID number starting from S0001 to S6280. After applying the Mahalanobis distance, the ellipse seen in Figure 1 was formed by using the measurements of PTH and adjusted calcium from the index date (single measurement of each variable per patient). In total, 5574 patients were inside the ellipse and were considered as 'normal' while the rest were outliers. Twenty-two patients fulfilled the criteria for NHYPO. The evaluation of their medical files excluded four patients. Three patients were excluded due to non-PTH-induced hypercalcaemia and S0051 due to myeloma, while S1743 and S5588 due to metastatic cancer. S0756 was excluded because the results extracted by the IT department could not be confirmed.

The group of provisional NHYPO patients consisted of eighteen patients (mean age 45, SD 16.4 years, 61% female). The prevalence for this population was 0.29% (95% confidence interval 0.18%-0.45%). None of these patients had previous anterior neck surgery or radiation. None of them was on active vitamin D. We noted that some patients had other conditions that could affect PTH results [thiazides n = 1, antiepileptic medications n = 4 (both conditions can increase PTH levels); one patient had coeliac disease, which can cause secondary hyperparathyroidism, and thalassaemia, which can cause functional hypoparathyroidism; and four patients were consuming increased levels of alcohol].

When studying the natural history, two patterns were identified (Figure 2): persistent normocalcaemia (67%) and intermittent hypocalcaemia (28%). One patient only had one measurement of calcium during the follow-up period (S5738). The minimum, maximum and

average values of the adjusted calcium were calculated for each patient, and the graphs of the means and the range of values were drawn (Figure 3). There were no statistical differences in these two groups in terms of age, gender distribution, average adjusted calcium and PTH levels ($P > .05$). In three of the patients with intermittent hypocalcaemia, the observed decreases in calcium could be explained (the most common cause was vomiting). One patient had one measurement of low calcium with no apparent reason explaining the results. Finally, one patient had one measurement of low calcium during an epileptic seizure, one linked to low vitamin D levels and a third one where no obvious reason for hypocalcaemia was identified.

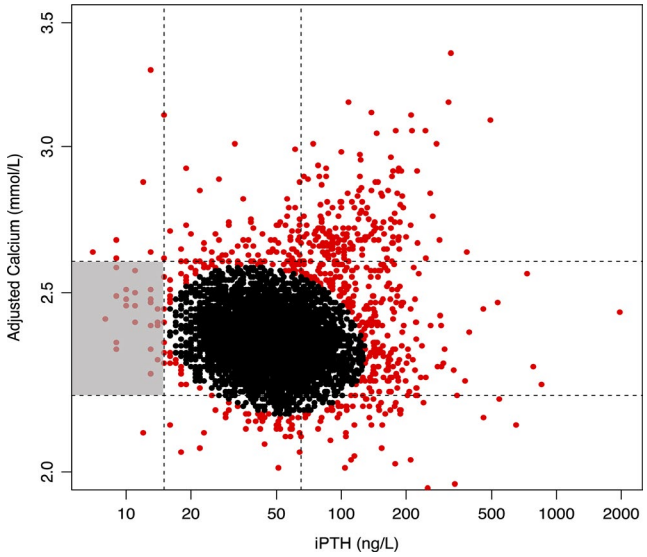

FIGURE 1 Data results from adjusted calcium and PTH. The ellipse was formed using a statistical method (Mahalanobis distance) to identify 'normal' subjects (black dots) and 'abnormal' ones (red dots). The laboratory's reference range of both adjusted calcium and PTH (horizontal and vertical dashed lines, respectively) was used to identify patient categories. The shaded area includes patients with normocalcaemic hypoparathyroidism (NHYPO) [Colour figure can be viewed at wileyonlinelibrary.com]

When looking at the number of available PTH measurements, eight patients had only one measurement of PTH during their follow-up. Six patients had two measurements amongst which one was low, while one had both measurements below the reference range. Three patients had more than two measurements, with two of them having persistently low PTH on two occasions.

Only one patient from the whole population was found to have hypoparathyroidism. This patient had thyroidectomy and developed hypocalcaemia as a result of this. The patient recovered spontaneously after a few months. The control population group consisted of 300 subjects (mean age 67, SD 15.6 years, 71% female). The characteristics of the two groups on the index date are summarized in Table 1. There were statistically significant differences in the age and BMI of the two groups; NHYPO patients were younger and had lower BMI. The gender distribution did not differ between the groups. Patients with NHYPO had significantly lower PTH and higher phosphate. Alkaline phosphatase and vitamin D levels did not differ between the groups. The NHYPO group had lower age- and gender-adjusted BMD estimates.

Interestingly, the adjusted calcium on the index date was higher in the control population. However, after taking all the follow-up measurements into account, the mean adjusted calcium was found to be similar in the NHYPO group compared with the control group (2.34 and 2.35 mmol/L for NHYPO and control group, respectively, $P = .496$). The variability of calcium in the NHYPO group was significantly higher than the control group [within-subject SD 0.096 (95% CI 0.085, 0.108) and 0.083 (95% CI 0.080, 0.085) mmol/L, respectively]. After taking all the follow-up measurements of PTH into account, the mean PTH

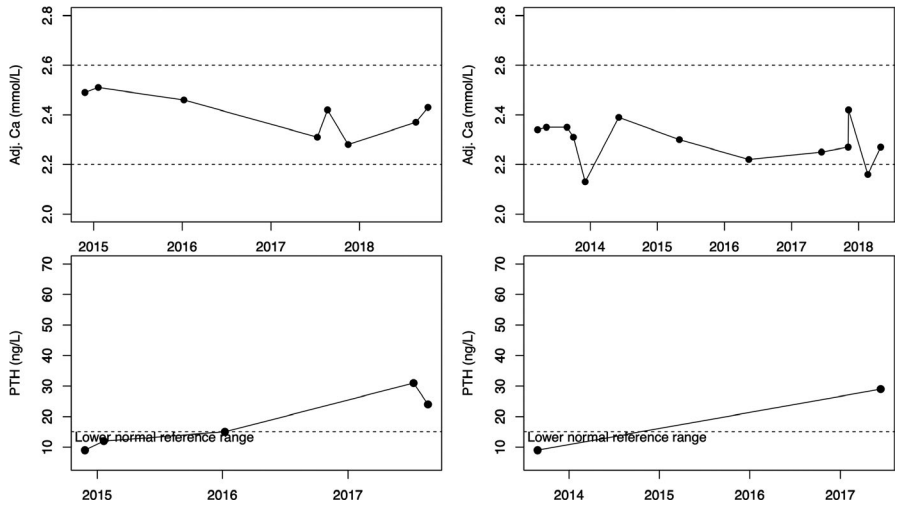

FIGURE 2 The two patterns identified in patients with normocalcaemic hypoparathyroidism when studying the natural history of adjusted calcium. Persistent normocalcaemia (left top figure, patient S2157) and intermittent hypocalcaemia (right top figure, patient S0161). The dotted lines represent the normal range for adjusted calcium. Both patients were on calcium and vitamin D supplements. The bottom graphs represent the variability of parathyroid hormone (PTH). None of the two patients maintained low parathyroid hormone throughout their follow-up. The increase in PTH observed in the patient on the left could be due to the initiation of zoledronic acid. The dotted line represents the lower normal of the reference range for PTH. Adj.Ca: adjusted calcium

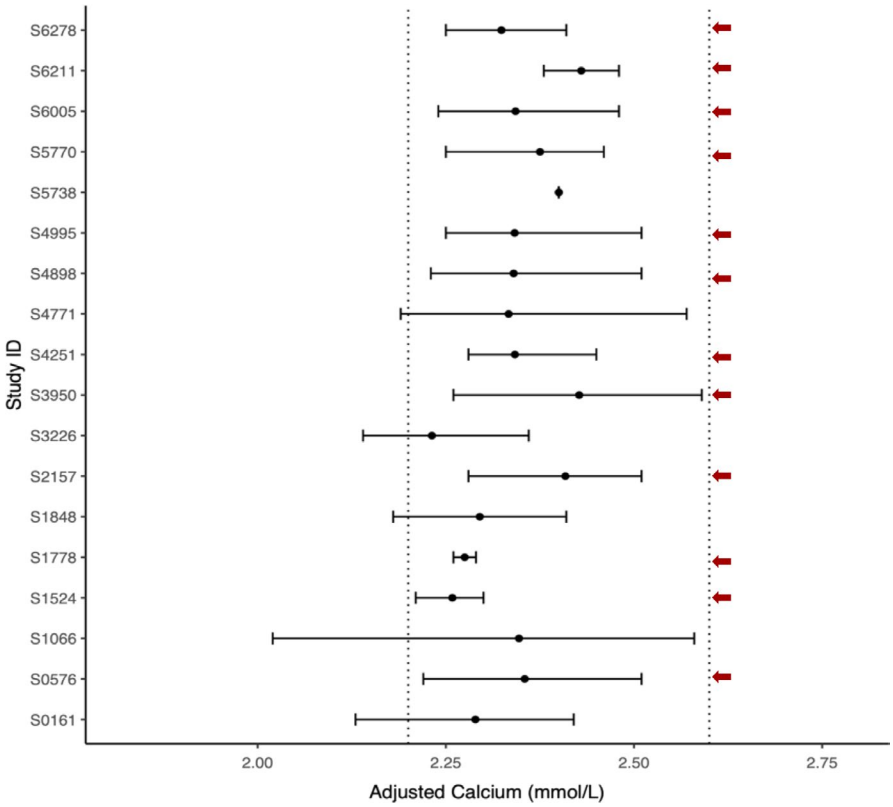

FIGURE 3 Means and range of values of different analytes in the 18 NHYPO patients. Out of them, only 67% had persistent normocalcaemia (shown in the red arrows). One patient had only one measurement available. The dashed lines represent the reference range for adjusted calcium, NHYPO: normocalcaemic hypoparathyroidism [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Characteristics of the two groups on the index date

	Control (n = 300)	NHYPO (n = 18)	*P* value
Female (%)	214 (71)	11 (61)	.354
Age (y)[b]	70 (20)	47 (24)	**<.001**
BMI (g/cm^2)[c]	25.6 (25.0-26.3)	22.6 (20.5-24.6)	**.020**
PTH (ng/L)[c]	42.5 (40.8-44.1)	11.1 (10.3-11.9)	**<.001**
Adjusted calcium (mmol/L)[a]	2.37 (0.08)	2.43 (0.09)	**.006**
Phosphate (mmol/L)[a]	1.12 (0.18)	1.26 (0.18)	**.003**
Alkaline phosphatase (IU/L)[b]	78 (37)	93 (36)	.059
25(OH)D (nmol/L)[b]	78.9 (32.9)	78.3 (61.1)	.561
Z-score spine[a]	−0.2 (1.7)	−1.5 (1.2)	**<.001**
Z-score neck[a]	−0.4 (1.0)	−1.1 (1.0)	**.011**

Note: The bold letters show the significant differences.

Abbreviations: BMI, body mass index; PTH, parathyroid hormone; NHYPO, normocalcaemic hypoparathyroidism.

[a]Shown as mean (standard deviation).

[b]Shown as median (interquartile range).

[c]Results from multiple linear regression analysis after adjusting for age, weight and gender.

was found to be lower in the NHYPO compared with the control group (15.8 and 48.0 ng/L, respectively, $P < .001$).

4 | DISCUSSION

Normocalcaemic hypoparathyroidism is a disorder characterized by low PTH and normal calcium on which limited information is available. To our knowledge, this is the first study of the prevalence in a tertiary centre and also the first study of the natural history of this disease; previous studies only showed results from two timepoints. We retrospectively evaluated 6280 patients attending a referral centre and identified eighteen patients with NHYPO on the index date (prevalence 0.29%). Out of them, only 67% had persistent normocalcaemia. The number of PTH measurements on these patients was limited, and we could only confirm persistently low PTH in one patient.

The prevalence of NHYPO has been studied previously in the community. Palermo et al studied the prevalence in 2419 older (55-79 years old) and 258 younger (30-40 years old) women from five European cities for the Osteoporosis and Ultrasound Study (OPUS) and identified 57 subjects with NHYPO (prevalence 2.4%), using a similar approach as in our study. In order to get the different categories described above, they used the reference range for adjusted calcium; for PTH, they used the geometric mean of the reference range, which probably explains the higher baseline prevalence presented in their study.[4] We have adjusted this method and brought it closer to the everyday clinical practice, by using both the Mahalanobis distance and the reference range for both adjusted calcium and PTH. In the Palermo study, the adjusted calcium at baseline was similar to the control population, while PTH was significantly lower in the NHYPO group. Age, BMI and 25(OH)D were similar between the two groups. Six years later, the measurements were repeated once in 1416 subjects; only 0.6% of the initial population (1.1% of the ones that went into follow-up) expressed persistent characteristics of NHYPO.[4] Our study showed some differences in baseline characteristics, with NHYPO patients being younger and having a lower BMI and higher adjusted calcium than the control. The age inclusion criteria in the OPUS study were more strict and thus the difference in the results. We only found a higher adjusted calcium at the index date. When taking all the repeated measurements into consideration, the levels between NHYPO and control were similar. The cohorts differed as OPUS participants were randomly selected compared to our cohort in whom there was clinical concern about bone health.

Cusano et al studied two nonreferral populations, the Osteoporotic Fractures in Men (MrOS) and the Dallas Heart Study (DHS).[5] MrOS is an unselected community-based study in older men aged 65 years or older that had no bilateral hip fractures. Using the baseline values, they identified 26 participants (prevalence 1.1%) with NHYPO. They also found lower levels of PTH in the NHYPO group when compared to the group having normal PTH. The level of adjusted calcium was similar between the groups. They did not find a significant difference in age between the groups, unlike our study; however, they only included patients over 65 years. BMI was also similar between the groups, while in our study, NHYPO patients were slimmer. BMD results were similar.[5] Our study found lower Z-scores in the NHYPO population on the index date. One explanation for this could be the slightly lower BMI in this group. Another possible explanation could be the fact that younger patients are more likely to have causes of secondary osteoporosis and thus relatively more affected than the older population investigated. Interestingly, this study found significantly higher consumption of calcium supplements ≥1000 mg in the NHYPO group (54% vs 23% in the group with normal PTH). The dose of vitamin D supplements was similar between the groups.[5] This could be the explanation to the fact that the adjusted calcium at baseline was slightly higher in the NHYPO group, an observation also seen in our study.

DHS is a population-based cohort for the evaluation of cardiovascular disease.[5] They reported a prevalence of 1.9% (68 patients were identified) from the baseline measurements.[5] This study included a follow-up (for 2122 subjects), where a single measurement was performed eight years later; out of the 26 subjects with NHYPO that went into follow-up, none developed hypocalcaemia. Only two had persistent NHYPO (prevalence 0.09% of the population that went into follow-up). Most of them (20 out of 26) had normal PTH.[5]

Normocalcaemic hypoparathyroidism was previously characterized as a state of 'low bone turnover', as patients with this disorder were found to have lower bone ALP, collagen type 1 cross-linked C-telopeptide (CTX) and osteocalcin compared to the normal population but without a significant BMD change over time.[4] The authors suggested a critical evaluation of potential treatment for osteoporosis in these patients, as medications like bisphosphonates can suppress bone turnover further and exacerbate adynamic bone disease.[4] Moreover, studies with teriparatide did not improve BMD in patients with hypoparathyroidism.[13] The question of which treatment to use in this group of patients becomes more relevant in our study, as all the patients were identified during a laboratory investigation for secondary osteoporosis.

There were a limited number of PTH measurements throughout the patients' follow-up in our study; eight patients out of the eighteen identified as having NHYPO had only one measurement available. This suggests that physicians are not so concerned about finding a low level of PTH and they do not tend to follow this up further. However, this disorder could be the subclinical form of hypoparathyroidism. Moreover, these patients might be more prone to developing hypocalcaemia after they receive medications that can affect calcium levels (eg bisphosphonates, loop diuretics and denosumab) or after they develop common symptoms; in our population, three of the NHYPO patients had incidence of hypocalcaemia due to vomiting. Interestingly, some episodes of hypocalcaemia in our patients could not be explained. Therefore, the low levels could be theoretically attributed to the variability of calcium. A concern is that hypocalcaemia can be a cause of cardiac arrhythmias and epileptic seizures.[14] One of the patients from this population had low levels of calcium during an epileptic fit.

Interestingly, four of our patients were known to have epilepsy and were on treatment with antiepileptics which are known to cause an increase in PTH; however, a low level was found.[15] One patient was on thiazides and one patient had coeliac disease, both known causes of high PTH. The patient with coeliac disease also had thalassaemia, so PTH could have been low due to the iron load in the parathyroids, a known cause of hypoparathyroidism. Another four patients were consuming increased levels of alcohol, which has been reported to decrease the levels of PTH.[16] Unfortunately, magnesium was not available to check for hypomagnesaemia.

Further information on this disorder is needed before any official recommendations are made, but we think that NHYPO should be mentioned in any future guidelines on hypoparathyroidism as it is not mentioned in the current ones[17,18]; its pathophysiological counterpart, normocalcaemic hyperparathyroidism, is already part of international guidelines.[19] As mentioned before, there is no official definition for NHYPO, but we propose the following definition: normal calcium with low PTH should be confirmed on at least two

occasions, but normocalcaemia does not have to be persistent as long as the average level of calcium is normal; episodes of hypocalcaemia can be part of the presentation. As for hypoparathyroidism, we propose that NHYPO includes both idiopathic and functional forms of hypoparathyroidism.

More research should be performed to further characterize this population, ideally a prospective, long-term study with repeated measurements of calcium and PTH. The patients identified should then be further characterized with more dedicated studies of calcium metabolism. Genetic studies would also be of interest. An explanation for this disorder could be that it is a mild form of activating CaSR mutation which results in the alteration of the set point for PTH. A mutation on the CaSR was reported in patients with normocalcaemic hyperparathyroidism.[20]

This study describes the largest population ever studied to identify provisional NHYPO and provides data during a long follow-up period (5 years). It is the first study that provides data on the natural history with adjusted calcium measurements available on more than two timepoints. There are several limitations in this study. The patients studied were identified from a referral centre and they were evaluated for causes of secondary osteoporosis, so they might be different than the general population. The samples were not fasting, a tourniquet was used to take blood, ionized calcium and magnesium were not available, and there were not many repeated measurements of PTH. The PTH molecule is rapidly degraded, and it was difficult to exclude pre-analytical variations for an inappropriate low PTH level. This was a retrospective observational study, and the number of measurements varied from patient to patient. The persistence of the results could not be always confirmed. The interval between the measurements was not the same, as expected in a real-life setting. This limited the possibility of further analyses. The analysis for the within-subject SD did not consider the effect of time. Ideally, to give a more accurate estimate of the variance, a prospective observational study should be designed, having the same number of measurements for each patient at regular intervals. Despite the limitations, this study provided a guide to how adjusted calcium varies between the different groups described.

In summary, we retrospectively evaluated a referral population and found a low prevalence of patients with normocalcaemic hypoparathyroidism. The most common pattern was persistent normocalcaemia (67%), but there were patients that had intermittent hypocalcaemia. None developed persistent hypoparathyroidism. The clinical implication of this study is that if a patient has low PTH but normal serum calcium, they should have regular follow-up as they could become hypocalcaemic at some point and can have clinical consequences like epilepsy. The findings of normal calcium and low PTH have to be confirmed before a certain diagnosis is made. Further prospective studies are needed to characterize this group further.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

MS and RE designed the study. MS and RS acquired the data. MS, RJ and RE analysed and interpreted the data. MS drafted the manuscript. All authors revised the manuscript, approved the final manuscript and took responsibility for the integrity of the data analysis. The authors confirm that the manuscript is original and has not been submitted elsewhere. Each author acknowledges that he/she has contributed in a substantial way to the work described in the manuscript and its preparation.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Marian Schini https://orcid.org/0000-0003-2204-2095

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