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B-mode ultrasound assessment of carotid artery structural features in patients with normocalcaemic hyperparathyroidism

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Abstract

Introduction: Normocalcaemic hyperparathyroidism is a condition first defined in 2008, characterized by normal serum calcium and high parathormone levels. Although normocalcaemic hyperparathyroidism is considered to have a milder clinical picture compared to asymptomatic primary hyperparathyroidism, recent studies have shown that it may be associated with osteoporosis, insulin resistance, metabolic syndrome, and cardiovascular risk factors. Considering that normocalcaemic hyperparathyroidism may pose a cardiovascular risk in the setting of carotid atherosclerosis, we sought to examine the structural features of the carotid artery in patients with normocalcaemic hyperparathyroidism compared to a control group. Material and Methods: After excluding patients with hypertension, diabetes, and dyslipidaemia (other factors contributing to atherosclerosis), 37 (32 females, 5 males) patients with normocalcaemic hyperparathyroidism with a mean age of 51.2 ± 8 (min: 32, max: 66) years and 40 controls (31 females, 9 males) with a mean age of 49.3 ± 7.5 (min: 34, max: 64) years with normal serum albumin-corrected calcium and parathyroid hormone levels were included in the study. Structural features of the carotid artery including intima-media thickness (mean and maximum), lumen diameter, and the presence of plaque were assessed using B-mode ultrasound.
Results: On ANCOVA analysis corrected for atherosclerotic factors (body mass index, waist circumference, fasting plasma glucose, serum cholesterol, lipid, and blood pressure), greater mean intima-media thickness was found in patients with normocalcaemic hyperparathyroidism than in controls (0.65 mm *vs*. 0.59 mm, respectively) (p = 0.023). Maximum carotid intima-media thickness was also greater in patients with normocalcaemic hyperparathyroidism compared to controls (0.80 mm *vs*. 0.75 mm, respectively) (p = 0.044). The study groups did not show a significant difference in lumen diameter and the presence of carotid plaque. In addition, a negative correlation was found between parathormone (PTH) level and lumen diameter. Conclusion: The findings of this study show that as with asymptomatic primary hyperparathyroidism, normocalcaemic hyperparathyroidism may be associated with increased cardiovascular risk by predisposing to atherosclerosis. **(Endokrynol Pol 2023; 74 (1): 67–73)**

Key words: *normocalcaemic hyperparathyroidism; parathyroid hormone; carotid intima-media thickness; mean intima-media thickness; maximum intima-media thickness; lumen diameter*

Introduction

Recently, a distinct entity characterized by consistently normal serum total and ionized calcium (iCa) levels with elevated parathormone (PTH) levels in the absence of an identifiable underlying cause of PTH elevation has drawn attention, and the condition has been defined as normocalcaemic hyperparathyroidism (nHPT) by the Third International Workshop on the Management of Asymptomatic Primary Hyperparathyroidism in 2008 [1]. It is debated whether this represents the initial phase of primary hyperparathyroidism (pHPT) or is due to some other conditions that cause PTH elevation [2–5]. Therefore, to exclude the causes of secondary hyperparathyroidism (sHPT), iCa and 25-hydroxy-vitamin D (25-OH vit D) levels should be assessed and confirmed to be within the normal range. In fact, it is even recommended that the 25-OH vit D level be raised above 30 ng/mL (75 nmol/L) [6]. Confirmation of a diagnosis of nHPT requires normal serum calcium (sCa) levels and elevated PTH level measured on at least on 2 occasions after excluding the causes of sHPT [7].

Clinical relevance of normocalcaemic hyperparathyroidism

Although it is considered that nHPT has a milder clinical course than asymptomatic pHPT, recent studies have shown that it may be associated with insulin resistance, metabolic syndrome (MetS), osteoporosis, and cardiovascular risk factors [8–12]. Several recommendations

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on the management of nHPT have been included in the guidelines at the 4th International Consensus Meeting held in 2013. Moreover, at the end of the guideline, nHPT has been listed among the top areas that warrant further research over the next 5 years [7].

Association of elevated serum calcium and parathyroid hormone levels with cardiovascular risk

Studies in patients with pHPT have shown that increased levels of both sCa and PTH have effects on cardiac myocytes and vascular smooth cells. In addition, it has been suggested that pHPT increases the risk of cardiovascular disease by causing hypertension, by promoting atherosclerosis through vascular calcification and remodelling, and by inducing the development of MetS via its effects on glucose metabolism and insulin resistance [13–15].

Carotid intima-media thickness (CIMT) is considered as a marker for early detection of cardiovascular risk, and the measurement of CIMT with B-mode ultrasound (US) imaging is a practical and non-invasive technique that has long been used in clinical studies for this purpose. Carotid mean intima-media thickness (mIMT) is known to be strong predictor of systemic atherosclerosis [16–18]. In several studies, increased CIMT has been demonstrated in patients with pHPT [19–22]. Apart from a CIMT study from Turkey by Cansu et al. involving a small number of patients with pHPT and nHPT, there are almost no studies that examined CIMT in patients with nHPT [23].

For this reason, keeping in mind that nHPT may pose a risk for cardiovascular disease by predisposing to carotid atherosclerosis, we sought to determine the structural features of the carotid artery including mean (mCIMT) and maximum intima-media thickness (MCIMT) and lumen diameter (LD), and the presence of carotid plaque (CP) in patients with nHPT versus control subjects using B-mode ultrasound imaging.

Material and methods

Patients

This study was conducted at the Endocrine and Metabolism Disorders outpatient clinic of Tekirdag Namik Kemal University Medical Faculty (Türkiye) between 4 January 2021 and 31 March 2022. Fifty patients aged 18 years or older with nHPT and normal albumin-corrected Ca (cCa) and iCa values obtained on 2 occasions at least 3 months apart, elevated PTH levels, mean estimated glomerular filtration rate (eGFR) > 60 mL/min/1.73 m², 25-OH vit D3 level > 30 ng/mL, no renal hypercalciuria and malignancy, and without any disease that could affect Ca and PTH metabolism and 50 age- and sex-matched control subjects with normal cCa and PTH were included in the study.

Smoking status and family history of cardiovascular disease were questioned. All participants underwent detailed physical examination. Height and body weight measurements were obtained, and body mass index (BMI) was calculated in kg/m². Waist circumference (WC) was measured at the superior border of the iliac crest. Systolic and diastolic blood pressure (BP) measurements were obtained from both brachial arteries after at least 5 minutes of rest and 2 readings of systolic and diastolic BP were averaged separately.

Comorbidities

Comorbidities such as diabetes mellitus (DM), hypertension (HT), and hyperlipidaemia (HL) were noted by taking detailed history from the patient and control groups. Patients taking medications for DM, HT, and HL were considered as having comorbidities. Thirteen (26%) patients with nHPT and 10 (20%) control subjects had comorbidities. Because these comorbidities also play a key role in the development of atherosclerosis, 13 (8 females, 5 males) patients in the nHPT group and 10 (6 females, 4 males) control subjects were excluded from the study, and the results were analysed for the remaining subjects. Ultimately, the results of 37 patients from the nHPT group [32 (86%) females and 5 (14%) males] and 40 control subjects [31 (78%) females and 9 (22%) males] were included in the evaluation.

Laboratory investigations

The laboratory parameters tested and the reference range for each parameter were as follows: serum total Ca concentration and 24-hour urine Ca excretion, phosphorus (P), PTH, alkaline phosphatase (ALP), fasting plasma glucose (FPG), creatinine, total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), free triiodothyronine (FT3), free thyroxine (FT4), and thyroid-stimulating hormone (TSH) concentrations were measured with a Cobas C8000 autoanalyzer (Roche Diagnostics, Mannheim, Germany). LDL-C was estimated using the Friedewald formula.

sCa, reference range for adults: 8.6–10.0 mg/dL; and intra- and inter-assay CV: 0.4–2.0% and 0.9–2.5%, respectively. sCa was adjusted for hypoalbuminaemia using the following formula cCa = [0.8 × (4.0 − albumin) + serum calcium].

24-hour urine Ca excretion (reference range:100–300 mg/24 h), intra- and inter-assay CV: 0.9–23.0% and 1.1–1.3%, respectively.

Molybdate UV method was used for phosphorus assay. Phosphorus reference range for adults: 2.5–4.5 mg/dL; and intra- and inter-assay CV: 0.6–0.7% and 1.2–1.4%, respectively.

Intact PTH was measured with electrochemiluminescence immunoassay "ECLIA" method using a Cobas C8000 autoanalyzer (Roche Diagnostics, Mannheim, Germany). Reference range: 15–65 pg/mL; intra- and inter-assay CV: 1.1–2.0% and 2.5–3.4%, respectively.

25-OH vit D3 was tested using ultra-performance liquid chromatography (UPLC) method on Thermoscientific Ultimate 3000 analyser (desirable range: 30–50 ng/mL, intra- and inter-assay CV: 2.0–11.0% and 2.0–5.9%, respectively).

ALP was measured using colorimetric assay (reference value: 40–129 U/L for males and 35–104 U/L for females; intra- and inter-assay CV: 0.6–0.7% and 1.7–2.4%, respectively).

Creatinine was analysed using kinetic colorimetric assay based on the Jaffé method. (reference range: 0.50–0.90 mg/dL for females and 0.70–1.20 mg/dL for males; and intra- and inter-assay CV: 1.1–2.1% and 2.2–3.5%, respectively). eGFR was calculated with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula.

Carotid artery intima-media thickness and lumen diameter measurement:

Carotid artery ultrasound (US) imaging was performed in all subjects using high-resolution B-mode ultrasound (ACUSON 2000; Siemens, United States, Inc.) with a 7.5-MHz probe. Carotid artery US imaging was performed on all subjects by a trained medical doctor (C.A.) who was blinded to patients or controls.

The right and left common carotid arteries were visualized and recorded at the end-diastole longitudinally, 20 mm distally from each common carotid artery, proximal to the dilation of the bulb. CIMT was defined as the distance between the lumen-intima and the media-adventitia interfaces, and the lumen diameter (LD) was defined as the distance between lumen-intimal edges [24]. Three separate measurements were obtained for LD and intima-media thickness (IMT) from each carotid artery. Mean and maximum IMT measurements were taken from the posterior wall of the carotid artery. mCIMT represents the mean value of all 3 measurements from each common carotid artery. MCIMT was the highest IMT measurement for each common carotid artery. Intima-media thickness greater than 1.3 mm in any segment of the carotid arteries was defined as plaque [25].

Statistical analyses

Statistical analyses were performed using SPSS v22.0 (IBM Corp., Armonk, NY, United States). Continuous variables were expressed as mean and standard deviation (SD), and categorical variables were expressed as frequency and percentage. The Shapiro–Wilk test was used to check whether the variables followed a normal distribution. Student's *t*-test and Mann–Whitney U tests were used for continuous variables, and χ^2 and Fisher's exact tests were used for categorical variables. Pearson correlation analyses were conducted to determine correlations of cCa, P, PTH with mIMT, MIMT, and LD. Analysis of covariance (ANCOVA) was performed to remove the effects of confounding variables such as BMI, WC, glucose, lipids, and BP. Results were reported as mean and 95% confidence interval (CI). Statistical significance was set at $p < 0.05$.

Ethical issues

The study was approved by the local Ethics Committee (Decision no. 2020.09.01.09) and conducted in accordance with the principles laid out in the Declaration of Helsinki. Written informed consent was obtained from all subjects included in the study.

Results

For this study, 37 patients (32 females, 5 males) with nHPT with a mean age of 51.2 ± 8 years (min: 32, max: 66) were included in the nHPT group, and 40 healthy subjects (31 females, 9 males) with a mean age of 49.3 ± 7.5 years (min: 34, max: 64) were included in the control group. Age and sex distribution was similar between the nHPT and control groups (Tab. 1).

Mean BMI and WC values were higher in the nHPT group than in the control group (BMI: 31.1 *vs.* 28.5 kg/m^2 and WC: 99.6 *vs.* 91.9 cm, respectively). Systolic and diastolic blood pressure (BP) measurements were similar in both groups. Among laboratory values, cCa and PTH values were higher and the phosphorus (P) level was lower in the nHPT group, compared to control group (Tab. 1). The mean 25-OH-vitamin D level was 35.1 ng/mL in the nHPT group, which was similar with that of control group. Mean eGFR was > 90 mL/min/1.73 m^2 in both groups. 24-hour urine Ca excretion was within normal range in both groups. There were no significant differences between the 2 groups in terms of FPG, lipid parameters, transaminases, and thyroid function tests (Tab. 1).

Family history of cardiovascular disease (CVD) was present in 2/37 (5.4%) patients in the nHPT group and absent in control subjects. All nHPT patients were non-smokers, whereas 5/40 (12.5%) controls were smokers.

Considering the higher WC and BMI in the nHPT group, as shown in Table 1, an analysis of covariance was first conducted for WC and BMI and then for other factors that are known to play a role in the development of atherosclerosis, including FPG, TC, HDL-C, LDL-C, and TG levels and systolic arterial blood pressure (SABP) and diastolic arterial blood pressure (DABP). After controlling for the effects of the atherosclerotic risk factors, the lumen diameter was not different between the groups, whereas increased mCIMT and MCIMT values were found in patients with nHPT compared to the control group (Tab. 2).

When the presence of CPs was examined, 6/37 (16.2%) nHPT patients and 7/40 (17.5%) controls were found to have CPs, with no significant difference between the 2 groups. The difference was still non-significant after correcting for WC, BMI, FPG, TC, LDL-C, HDL-C, TG, SABP, and DABP ($x^2 = 0.023$, $p = 0.081$).

The logistic regression model with covariates of WC, BMI, FPG, TC, LDL-C, HDL-C, TG, SABP, and DABP was non-significant for the presence of CP.

Following an analysis of the associations of cCa, P, and PTH levels with mIMT, MIMT, and LD, a negative correlation was found between PTH and LD ($r = –0.375$, $p = 0.01$, Fig. 1).

Discussion

In this study, as expected, cCa and PTH levels were higher in the nHPT group versus controls, because PTH was already elevated compared to reference values despite normal cCa levels in these patients. In addition, although phosphorus levels were within the normal range in the nHPT group, they were significantly lower than those of control subjects. In our study, 24-hour urine Ca excretion was specifically considered in the patient group for the differential diagnosis of nHPT. 24-hour urine Ca excretion was not significantly increased in nHPT patients in comparison to controls. However, phosphorus excretion in urine was not assessed. Nevertheless, because it is theoretically known that PTH has Ca-sparing and phosphaturic actions in renal tubules, the relatively low phosphorus and high Ca levels observed in nHPT patients versus controls can be interpreted as increased activity of PTH. This was an expected finding for the patients with nHPT when compared to control subjects.

In the present study, mean mCIMT and MCIMT values were also higher in the nHPT group in com-

Table 1. *Characteristics of normocalcaemic hyperparathyroidism (nHPT) patients and controls*

Variable	nHPT (n = 37)	Control (n = 40)	p
Age [years]	51.2 ± 8 (n = 37)	49.3 ± 7.5 (n = 40)	0.289
Age [years], females	50.9 ± 8.4 (n = 32)	49.4 ± 7.5 (n = 31)	0.442
Age [years], males	53.2 ± 7.4 (n = 5)	49.1 ± 7.8 (n =9)	0.356
BMI [kg/m^2]	31.1 ± 5.4	28.5 ± 5.8	0.046
WC [cm]	99.6± 10.9	91.9 ± 11.4	0.003
SABP [mm Hg]	128± 14	128 ± 21	0.921
DABP [mm Hg]	82 ± 9	82 ± 13	0.998
cCa [mg/dL]	9.7 ± 0.3	9.4 ± 0.3	< 0.001
P [mg/dL]	3.2 ± 0.6	3.6 ± 0.6	0.009
PTH [pg/mL]	76.0 ± 34.8	47.6 ± 29.4	< 0.001
ALP [IU/L]	78 ± 26	69 ± 24	0.127
25-OH vit D [ng/mL]	35.1 ± 5.9	33.6 ± 6.1	0.284
24-h U Ca [mg/24 h]	182 ± 52	205 ± 86	0.695
Crea [mg]	0.7 ± 0.2	0.7 ± 0.1	0.651
eGFR [mL/min/1.73 m^2]	99 ± 10	102 ± 7.5	0.186
Glucose [mg/dL]	96 ± 8	95 ± 9	0.324
TC [mg/dL]	213 ± 37	212 ± 41	0.906
LDL-C [mg/dL]	131±32	126 ± 33	0.537
HDL-C[mg/dL]	54±13	55 ± 14	0.837
TG [mg/dL]	146 ± 65	152 ± 76	0.871
AST [IU/L]	20 ± 6	18 ± 7	0.274
ALT [IU/L]	23 ± 12	20 ± 10	0.240
TSH [mIU/L]	2.4 ± 1.9	2.1 ± 3.2	0.324
FT4 [pg/mL]	1.2 ± 0.2	1.2 ± 0.2	0.779
FT3 [mcg/dL]	3.1 ± 0.7	3.0 ± 0.5	0.467

All values shown are mean ± standard deviation (SD); BMI — body mass index; WC — waist circumference; SABP — systolic arterial blood pressure; DABP — diastolic arterial blood pressure; n — number of subjects; cCa — albumin-corrected calcium; P — phosphorus; PTH — parathyroid hormone; ALP — alkaline phosphatase; 25-OH vit D — 25-OH-vitamin D; 24-h U Ca — 24-hour urine Ca excretion; Crea — creatinine; eGFR — estimated glomerular filtration rate; TC — total cholesterol; LDL-C — low-density lipoprotein cholesterol; HDL-C — high-density lipoprotein cholesterol; TG — triglyceride; AST — aspartate aminotransferase; ALT — alanine aminotransferase; TSH — thyroid stimulating hormone, FT4 — free thyroxine; FT3 — free triiodothyronine; p — p-value

Table 2. *Comparison of carotid intima-media thickness (mean and maximum) and lumen diameter between normocalcaemic hyperparathyroidism (nHPT) and control groups*

	nHPT (n = 37)	Control (n = 40)	p
mCIMT [mm]	0.65 (0.61–0.68)	0.59 (0.55–0.62)	0.023
MCIMT [mm]	0.80 (0.77–0.84)	0.75 (0.71–0.78)	0.044
LD [mm]	5.4 (5.2–5.7)	5.5 (5.2–5.7)	0.621

All values shown are mean [95% confidence interval (CI)]; mCIMT — mean carotid intima-media thickness; MCIMT — maximum carotid intima-media thickness; LD — lumen diameter; n — number of subjects; p — p-value. *Means were adjusted for waist circumference (WC), body mass index (BMI), fasting plasma glucose (FPG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglyceride (TG), systolic arterial blood pressure (SABP), and diastolic arterial blood pressure (DABP) (ANCOVA). Covariates appearing in the model were evaluated at the following values (WC = 95.6 cm, BMI = 29.8 kg/m^2, FPG = 96 mg/dL, TC = 212 mg/dL, LDL-C = 128 mg/dL, HDL-C = 54 mg/dL, TG = 161 mg/dL, SABP = 128 mmHg, DABP = 82 mmHg).

parison to controls. Although previous studies reported an association between pHPT and increased CIMT, there are no studies in the literature that focused on the relationship between nHPT and CIMT in a sufficiently large sample, except for the study by Cansu et al. in a small number of patients [23]. The primary aim of our study was to investigate whether nHPT affects the structural features of the carotid artery. Because nHPT is generally regarded to have a milder clinical course than asymptomatic pHPT, it is a remarkable find-

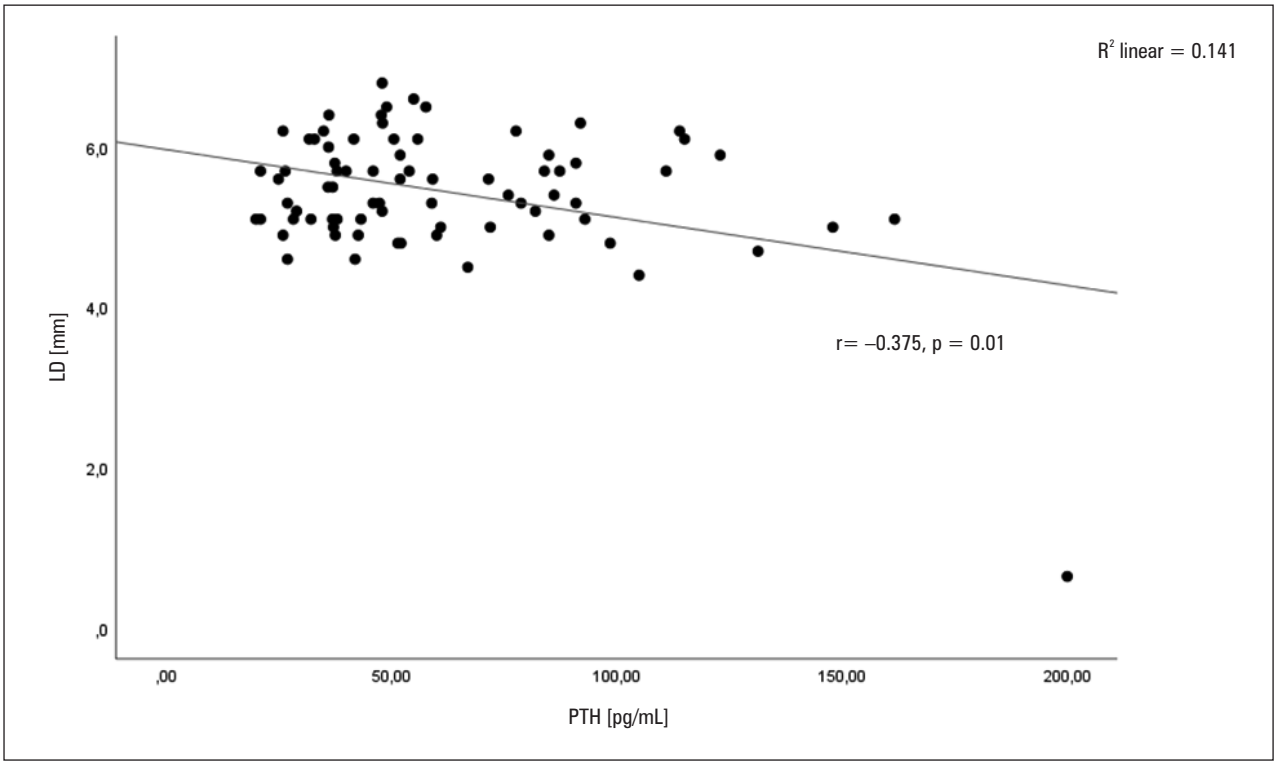

Figure 1. *Correlation between parathyroid hormone (PTH)levels and lumen diameter (LD)*

ing that both mCIMT and MCIMT were increased in nHPT patients compared to controls, as demonstrated by B-mode ultrasound imaging.

In our study, mCIMT values were 0.66 mm in the nHPT group and 0.59 mm in the control group. In the Turkish study by Cansu et al. involving 17 patients with pHPT, 16 patients with nHPT, and 15 healthy controls, mean CIMT was estimated during ultrasonography using quality intima-media thickness (QIMT) analysis software. The authors reported mean carotid quality intima-media thickness (CQIMT) values of 0.60 mm for the pHPT group, 0.59 mm for the nHPT group, and 0.53 mm for the control group [23]. These values are slightly lower than those found in our study. This may be related to the use of a different technique for the measurement of CIMT in that study. However, it seems that CIMT values (both mIMT and MIMT) of the Turkish population are lower than those reported by Walker et al. (0.96 mm for pHPT patients *vs.* 0.91 mm for controls) and also compared to the reference range of 0.70–0.90 mm used in that study [20]. It should be noted that our study had a larger sample size than that of Cansu et al. For this reason, it is not possible to take the CIMT values reported by Cansu et al. as a reference, and they can only be used for an approximate estimate.

In a study with a sample size similar to that of our study, which investigated CIMT in Turkish patients with inflammatory bowel disease, mCIMT and MCIMT were 0.74 mm *vs.* 0.66 mm and 0.86 *vs.* 0.76 mm in the patient and control groups, respectively [26]. These values closely match the mCIMT and MCIMT values found in the current study and give an idea about the CIMT of the Turkish population. Additionally, in a Czech study examining the prevalence of prehypertension in different dyslipidaemic phenotypes and their association with CIMT, mean CIMT diameters were 0.59, 0.66, 0.67, and 0.72 mm in different subgroups [27]. These values from a Central European country are similar to what we found.

In our study, BMI and WC were also higher among patients with nHPT in comparison to controls, and this is an interesting finding. When we were recruiting control subjects, we were careful to choose age- and sex-matched individuals with normal cCa and PTH levels. We did not consider matching controls with patients in terms of BMI and WC. There may be 2 reasons why BMI and WC were higher in the nHPT group: 1 — the control group was created without taking BMI and WC into consideration, and 2 — the nHPT group of our study consisted of overweight patients with a significantly greater waist circumference, resulting in a predisposition to abdominal obesity, as shown in other studies. In a prospective study by Yener-Ozturk et al. assessing MetS parameters in patients with nHPT, the subjects had comparable BMI. In the same study, mean WC values were 103.88 cm in the nHPT

group, 106.54 cm in the pHPT group, and 97.00 cm in the control group. Waist circumference of the nHPT patients was similar to that of pHPT patients but significantly greater than that of the controls [10]. In line with Yener-Ozturk et al. study, WC values were 99.6 cm in the nHPT group versus 91.9 cm in the control subjects in our study.

In a cohort study by Ahlström et al., PTH level was positively correlated with BMI and WC in patients with pHPT. This is consistent with the high BMI and WC results found in our study [11].

In the current study, considering that BMI and WC may have confounding effects in the nHPT group, we compared patient and control groups after correcting for these factors using ANCOVA. Although no difference was initially observed between nHPT and control groups with respect to FPG, lipids, and BP, we again found higher mCIMT and MCIMT in the nHPT group versus controls on ANCOVA, when the 2 groups were compared after correcting for atherosclerotic risk factors including WC, BMI, FPG, lipid values, and BP. This indicates that nHPT may be associated with the risk of atherosclerosis even after adjusting for confounding factors. In line with Nuzzo et al. study reporting increased CIMT in pHPT patients even when left ventricular diameter and features and BP levels were normal [19], a significant difference was found between patient and control groups in terms of CIMT despite comparable BP values in the present study.

There is variability across studies in the type and reporting of IMT measurements made for the assessment of CIMT. Different approaches have been used, including the use of only mCIMT or MCIMT for single measurements, and reporting mean mCIMT or mean MCIMT values separately for multiple measurements. Also, studies differ in the definition of plaque, whether plaques were included in the IMT measurements, and arbitrary cut-off points for CIMT used for risk prediction. Because the atherosclerotic process has a focal nature, IMT measurements from one site can vary greatly from those obtained another site. Therefore, measuring CIMT from one site may only lower the sensitivity of identifying atherosclerotic changes [28]. For this reason, we obtained 3 measurements on each occasion and recorded the measurements as both mCIMT and MICMT. We also recorded the LD and the presence of CP. In this way, we planned to compare our results to those previously reported as mCIMT or MCIMT. Although mCIMT has been used more commonly in former, similarly designed studies and made comparisons accordingly, we decided to also share our MCIMT results to shed light on future studies.

Of note, a negative correlation was found between PTH and LD in our study, despite the absence of a significant difference between nHPT and control groups in terms of mean LD values. This shows that as the PTH level increases, the LD decreases. Considering that the cCa and iCa values of our nHPT group were within the normal range and PTH levels were lower compared to those of the pHPT population, the correlation between PTH and LD is remarkable. There are several studies that support the role of PTH in the development of atherosclerosis in pHPT, and others implicating Ca in that process [29, 30]. In a cross-sectional, population-based study by Kamycheva et al., elevated PTH was reported as a risk factor for cardiovascular disease in patients with normal Ca values and creatinine values below 1.21 mg/dL who were not receiving diuretics [31]. However, that study included patients with nHPT as well as patients who might have sHPT. Despite this, it is noteworthy that elevated PTH contributes to increased CVD risk. Likewise, in 2 studies by Rashid et al., it was reported that PTH promotes atherogenesis in the endothelium by increasing the expression of vascular endothelial growth factor and stimulating protein kinase activity [32, 33]. In our study, while no correlation was observed between cCa and structural features of the carotid artery, a correlation was found between PTH and LD only. This suggests that PTH has an effect on lumen diameter. Given the relationship between LD narrowing and atherosclerosis, this also demonstrates the atherosclerotic effect of nHPT.

It is possible to explain the absence of a negative correlation between PTH and LD in terms of mCIMT and MCIMT as follows: although the overall increase in CIMT as demonstrated by both mIMT and MIMT measurements did not show a correlation with PTH in the nHPT group, PTH contributes to CV risk through LD narrowing. Because MCIMT reflects the maximum measurement value and mCIMT indicates the mean measurement value for intima-media thickness in a patient, naturally, both measures would show a similar association with PTH. The fact that PTH did not show an obvious correlation with mCIMT and MCIMT can be explained by the relatively small sample size. Further studies are needed to corroborate our findings.

Conclusion

Although there are a few studies on CIMT, a marker that predicts atherosclerosis, in patients with asymptomatic pHPT, there is an insufficient number of studies examining cardiovascular risk in nHPT patients, and most of them were of small scale. In this context, this is the first study to report on the association between nHPT and CIMT in 37 patients with pure nHPT. Studies

involving larger sample sizes in support of such a correlation are warranted.

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Conflict of interest

The authors declare that they have no conflict of interest.

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