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Assessment of Metabolic Syndrome Components in Patients with Normocalcemic Hyperparathyroidism: A Retrospective Study

ABSTRACT

Objective: Normocalcemic hyperparathyroidism is characterized by elevated parathormone levels persisting for 3 months or longer despite normal serum Ca levels. This study aimed to retrospectively compare the prevalence of individual metabolic syndrome components between patients with normocalcemic hyperparathyroidism and an age- and sex-matched control group.

Methods: Data of 82 normocalcemic hyperparathyroidism patients and 80 control subjects with normal parathormone and calcium levels were reviewed retrospectively. Those meeting 3 or more of the 2001 metabolic syndrome diagnostic criteria of the US National Cholesterol Education Program Adult Treatment Panel III were considered as having metabolic syndrome. Also, Turkish waist circumference cutoff values were used to identify abdominal obesity and to estimate the metabolic syndrome frequency.

Results: Considering that higher body mass index of normocalcemic patients would confound the analysis, analysis of covariance adjusted for body mass index was used to compare the groups, which showed increased waist circumference, waist/hip ratio, parathormone, 25 OH vitamin D3, fasting plasma glucose, and total cholesterol and low-density lipoprotein-cholesterol levels in normocalcemic hyperparathyroidism patients than controls. The prevalence of metabolic syndrome among normocalcemic hyperparathyroidism patients was 32.9% (22.5% in controls) using the National Cholesterol Education Program Adult Treatment Panel III criteria versus 34.1% (23.8% in controls) using the Turkish waist circumference cutoff values.

Conclusion: The percentage of patients meeting the metabolic syndrome criteria was higher compared to the control group. Even in the case of normocalcemic hyperparathyroidism, which is considered to be a milder condition, the prevalence of metabolic syndrome was relatively higher than in the control group, suggesting that normocalcemic hyperparathyroidism may be a cardiovascular risk factor by predisposing to metabolic syndrome.

Keywords: Body mass index, metabolic syndrome, normocalcemic hyperparathyroidism, waist circumference, waist/hip ratio

Introduction

Normocalcemic hyperparathyroidism (nHPT) is a newly defined clinical entity. As opposed to primary hyperparathyroidism (pHPT), serum total and ionized calcium (iCa) levels are in the normal range, whereas parathormone (PTH) levels exceed the normal reference range in nHPT.[1] It is still unclear whether nHPT has a milder clinical course than classical pHPT or is a condition presenting with the same types of complications as those seen in asymptomatic pHPT. However, recent studies have reported that similar to asymptomatic pHPT, nHPT is also associated with metabolic syndrome (MetS) and cardiovascular (CV) risk factors.[2-4] As elevated serum Ca (sCa) concentrations stimulate higher insulin levels by regulating intracellular free Ca concentrations, it has been suggested that sCa level is correlated with insulin resistance in pHPT.[5] Also, a link between insulin resistance and increased CV risk has been demonstrated.[6] An atherogenic metabolic profile accompanied by insulin resistance has been reported in patients with nHPT.[3,4]

Among the MetS diagnostic criteria proposed by various international bodies, those published by the US National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) and International Diabetes Federation (IDF) are most commonly used in clinical and population-based cohort studies. Although there are different criteria for the identification of MetS, all of them agree that the core components of MetS include abdominal obesity (increased waist circumference [WC]), insulin resistance, dyslipidemia, and hypertension.[7-9] The cut-off

Osman Alp Baykut[1]
Gülşah Elbüken[2]
Burcu Tokuç[3]
Sayid Shafi Zuhur[2]

[1]*Department of Internal Medicine, Tekirdağ Namık Kemal University Faculty of Medicine, Tekirdağ, Turkey*
[2]*Division of Internal Medicine, Department of Endocrinology and Metabolism, Tekirdağ Namık Kemal University Faculty of Medicine, Tekirdağ, Turkey*
[3]*Department of Medical Education, Tekirdağ Namık Kemal University Faculty of Medicine, Tekirdağ, Turkey*

Corresponding author:
Gülşah Elbüken
✉ gelbuken@nku.edu.tr

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value for the WC measurement used to evaluate abdominal obesity varies among ethnic groups and countries. There are 2 important studies from Turkey in which WC measurements were obtained from large samples. One of them is the Turkish Diabetes Epidemiology II study involving nearly 25 000 subjects, which defined central obesity based on WC cutoff values of 96 cm (females) and 100 cm (males).[10] A comprehensive study by Sonmez et al[11] showed WC cutoff values of 90 cm in women and 100 cm in men. The 2019 Guidelines for the Diagnosis and Management of Obesity of the Turkish Society of Endocrinology and Metabolism also recommend the use of WC thresholds of 90 and 100 cm for women and men, respectively.[12]

Metabolic syndrome is a CV risk factor since it plays a role in the development of atherosclerosis. There are published studies in the literature showing that the MetS components are more prevalent in patients with nHPT than in healthy controls.[2-4] This suggests that nHPT may be a risk factor for CVD or may contribute to CV risk factors. In light of the aforementioned data, we aimed to retrospectively compare the prevalence of individual MetS components between patients with nHPT followed at our clinic and age- and sex-matched control group without any disorders of Ca and PTH metabolism.

Materials and Methods

Subjects

This study was designed as a retrospective case–control study. Currently, there are about 90 patients with nHPT who are followed at our outpatient clinic. The data of these patients were retrieved from electronic medical records of our hospital over a period of 1 year (between April 21, 2021, and April 21, 2022) and 82 patients meeting the inclusion criteria were identified. Age and sex distribution of these patients were calculated, and a control group was formed, consisting of 80 randomly selected, age- and sex-matched patients with other diagnoses such as euthyroid nodular goiter and dyspepsia who presented to the internal medicine and endocrinology outpatient clinics. When selecting control subjects, apart from age and sex considerations, care was taken to include only those with Ca and PTH levels within the normal range. Body mass index (BMI), WC, blood pressure (BP), and laboratory investigations were not taken into account.

Inclusion criteria were age over 18 and less than 75 years, not being pregnant (for women), no liver or kidney disease, and absence of malignancy and other systemic disorders that could potentially affect Ca–PTH–vitamin D axis.

The diagnosis of nHPT was based on normal albumin-corrected Ca (cCa) and iCa values obtained at the outpatient clinic on at least 2 occasions 3 months apart, elevated PTH values, estimated glomerular filtration rate (eGFR) of >60 mL/min/1.73 m^2, 25-OH vitamin D3 level >30 ng/mL, in the absence of malabsorption, renal hypercalciuria, or malignancy and no use of medications that could affect Ca and PTH metabolism such as lithium and thiazide diuretics. Control group consisted of age- and sex-matched individuals with normal Ca and PTH levels who met the inclusion criteria listed above. None of the patients or controls were diagnosed with diabetes mellitus.

Materials and Methods

Data of the study population retrieved from the hospital's electronic medical records were reviewed retrospectively. Height, body weight, WC, hip circumference (HC), and BP measurement values were noted. Body mass index in kg/m^2 was calculated by dividing the weight in kilograms by the square of height in meters. Waist/hip ratio (WHR) was obtained by dividing the WC by the HC. Subjects fulfilling 3 or more of the NCEP-ATP III criteria were considered as having MetS.[8] In addition, Turkish WC cutoff values of >90 cm (women) and >100 cm (men) were used for this study to estimate the frequency of MetS.[12]

The study was approved by the Local Ethics Committee of Tekirdağ Namık Kemal University, Faculty of Medicine (date: March 30, 2021, no: 2021.69.03.09) and conducted in accordance with the principles laid out in the Declaration of Helsinki. Since this was a retrospective study, written informed consent was not obtained from the subjects.

Laboratory Investigations

Fasting plasma glucose (FPG) and lipid profile were obtained in the morning after at least 8-10 hours of overnight fasting. In order to avoid any effects of lipid-lowering drugs on lipid levels, lipid values from patients not on lipid-lowering drugs or off-therapy lipid values were included in the analysis. The same consideration also applied to control subjects.

Serum total Ca concentration and 24-hour urinary Ca excretion, phosphorus (P), uric acid, intact PTH, alkaline phosphatase (ALP), FPG, creatinine, total cholesterol (TC), high-density lipoprotein (HDL)-C, triglyceride (TG), aspartate aminotransferase (AST), alanine aminotransferase (ALT), free triiodothyronine (FT3), free thyroxine (FT4), and thyroid stimulating hormone (TSH) concentrations were measured with Cobas C8000 autoanalyzer (Roche Diagnostics, Mannheim, Germany). Serum calcium was corrected for hypoalbuminemia using the following formula: cCa = [0.8 × (4.0 − albumin) + serum calcium]. Molybdate ultraviolet (UV) method was used for phosphorus assay. 25-hydroxyvitamin D3 was tested using ultra-performance liquid chromatography method on Thermoscientific Ultimate 3000 analyzer. The estimated glomerular filtration rate was calculated using Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula. Low-density lipoprotein was estimated using the Friedewald formula: [TC- (HDL-C) − (triglyceride/5) in mg/dL].

MAIN POINTS

- Normocalcemic hyperparathyroidism (nHPT) has been a known entity for the last 10 years, and attention has been directed to cardiovascular and metabolic complications in this group of patients, apart from the classical complications of osteoporosis and nephrolithiasis. In this study, the frequency of metabolic syndrome was investigated retrospectively in patients with nHPT.
- The number of cases was 82, which is quite high considering the relatively low prevalence of nHPT.
- A unique aspect of the study is the use of Turkish waist circumference cutoff values along with the National Cholesterol Education Program Adult Treatment Panel III criteria.
- It is important that it reflects Turkish data in this patient population.
- It is noteworthy that the average waist circumference is high in nHPT patients.
- Although the frequency of metabolic syndrome in patients with nHPT was not higher than the prevalence of metabolic syndrome in the Turkish population, it was found to be higher than the control group.

Statistical Analyses

Statistical Package for Social Sciences software, version 22.0 (IBM Corp., Armonk, NY, USA) was used for statistical analyses. Whether the data were normally distributed was checked using kurtosis and skewness values (±1.5). The demographic and clinical characteristics of the subjects were summarized using descriptive statistics (number, percentage, mean, standard deviation). Independent samples *t*-test was used to compare the means between the groups. The chi-square test was used to analyze the sex ratio and MetS frequency between patient and control groups. Pearson correlation analysis was performed to examine the correlation between WC and PTH. An analysis of covariance (ANCOVA) was conducted to eliminate the confounding effect of BMI. The statistical significance level was set at $P < 0.05$ for all analyses.

Results

This retrospective study included a total of 82 patients with nHPT and 80 controls. 87.7% (n = 73) of the nHPT patients were female and 12.3% (n = 9) were male, and 87.5% (n = 70) of the controls were female and 12.5% (n = 10) were male. Patient and control groups were balanced in terms of age, age distribution, and sex ratio ($P >$ .05). While there was no difference between the groups with respect to mean height and body weight, nHPT group showed a significantly greater BMI (31.52 kg/m^2) than the control group (28.85 kg/m^2) (Table 1).

Since patients with nHPT had greater BMI than the control group and considering the potential effect of BMI on MetS components (WC, HC, BP, and FPG and lipid levels), an ANCOVA adjusted for BMI was performed. Patients with nHPT showed significantly greater mean WC and WHR values compared to control subjects. Mean systolic and diastolic BP values were not significantly different between the groups (Table 2). While mean cCa and P levels did not differ between the nHPT group and control group, mean PTH levels were significantly higher in the patient group, as expected. 25(OH)D3 levels were higher in the nHPT group compared to control group (Table 2). After adjusting for BMI, mean FPG of the nHPT group was significantly higher than that of control group. Likewise, mean TC and LDL-C levels were significantly greater in the patient group, but HDL-C and TG levels were comparable between the groups (Table 2).

Analysis of correlations between the variables showed a positive correlation between PTH and WC (Figure 1) and PTH versus FPG (Figure 2).

Table 1. Mean Age, Height, Body Weight, and Body Mass Index of nHPT and Control Groups

	nHPT (n = 82) Mean ± SD	Control (n = 80) Mean ± SD	*P*
Age (years)	59.63 ± 9.32 (min: 38, max: 75)	57.73 ± 6.74 (min: 42, max: 73)	.137
Height (cm)	158.13 ± 8.10	160.09 ± 7.63	.116
Body weight (kg)	78.87 ± 15.73	73.67 ± 12.09	.063
Body mass index (kg/m^2)	31.52 ± 6.45	28.85 ± 4.88	***.013***

nHPT, normocalcemic hyperparathyroidism; SD, standard deviation.
P values with statistical significance ($P < .05$) are indicated in bold and italics.

Table 2. Anthropometric Measurements, Blood Pressure, and Laboratory Values of nHPT* and Control Groups

	nHPT Mean ± SD (n = 82)	Control Mean ± SD (n = 80)	*P*
WC (cm)	105.54 ± 13.72	94.81 ± 14.56	***<.001***
HC (cm)	117.27 ± 13.22	110.56 ± 11.16	.074
WHR	0.90 ± 0.06	0.85 ± 0.08	***.001***
sBP (mmHg)	135.73 ± 20.64	131.12 ± 13.41	.442
dBP (mmHg)	83.72 ± 10.77	82.37 ± 9.17	.925
cCa (mg/dL)	9.21 ± 0.47	9.22 ± 0.27	.815
P (mg/dL)	3.44 ± 0.49	3.51 ± 0.47	.492
PTH (pg/mL)	104.86 ± 29.89	41.88 ± 10.51	**<.001**
ALP (IU/L)	77.02 ± 23.19	77.67 ± 34.94	.977
25(OH)D3(ng/mL)	31.06 ± 10.31	28.08 ± 10.03	***.017***
24-hour urinary Ca excretion (mg/24-h)	185.61 ± 135.72	171.78 ± 103.64	.765
Uric acid (mg/dL)	4.89 ± 0.92	4.57 ± 1.29	.157
FPG (mg/dL)	109.78 ± 18.39	96.58 ± 10.64	***<.001***
Creatinine (mg/dL)	0.77 ± 0.18	0.73 ± 0.17	.179
eGFR (mL/min/1.73 m^2)	97.74 ± 8.63	100.82 ± 14.90	.493
Total-C (mg/dL)	214.65 ± 46.09	192.51 ± 40.06	***.007***
LDL-C (mg/dL)	133.32 ± 36.97	111.91 ± 30.95	***<.001***
HDL-C (mg/dL)	54.81 ± 13.77	54.25 ± 13.91	.734
TG (mg/dL)	148.28 ± 62.87	130.31 ± 46.74	.147
TSH (mIU/L)	2.52 ± 1.28	2.11 ± 0.97	.300
FT4 (pg/mL)	1.28 ± 0.19	1.31 ± 0.34	.440
FT3 (µg/dL)	2.81 ± 0.44	2.90 ± 0.56	.312

25(OH)D3, 25-hydroxyvitamin D3; ALP, alkaline Phosphatase; BMI, body mass index; cCa, albumin-corrected calcium; dBP, diastolic blood pressure; FPG, fasting plasma glucose; HC, hip circumference; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; nHPT, normocalcemic hyperparathyroidism; P, phosphorus; PTH, parathormone; sBP, systolic blood pressure; SD, standard deviation; TG, triglyceride; Total-C, total cholesterol; WC, waist circumference; WHR, waist/hip ratio.
*Comparison of means adjusted for BMI on ANCOVA is shown.

When the 2 groups were evaluated in terms of the presence of the MetS components as per the NCEP ATP III criteria, a significant difference was observed only in the number and percentage of individuals with increased WC and FPG. No significant difference was found with respect to low HDL-C, elevated TG, or increased BP (Table 3).

Using the NCEP ATP III criteria, increased WC was found in 69 (84.1%) patients in the nHPT group versus 56 (70%) control subjects (Figure 3, left). However, using the Turkish WC cutoff values, 62 (75.6%) patients with nHPT showed increased WC versus 44 (55%) controls, and the difference was statistically significant (Figure 3, right).

When the groups were analyzed according to the presence or absence of MetS as per the NCEP ATP III criteria, nHPT group (32.9%, n = 27) showed a higher frequency of MetS compared to the control group (22.5%, n = 18) (Figure 4). Using the Turkish WC cutoff values for males and females, the number of individuals meeting the MetS criteria increased by 2-fold due to WC of 101 cm in 1 male each from nHPT and control groups. Again, the frequency of MetS

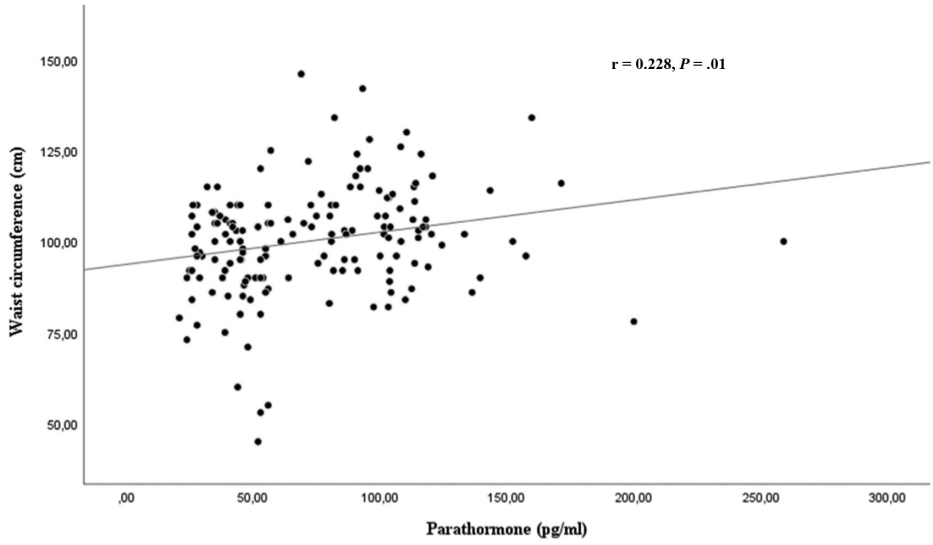

Figure 1. Correlation between parathormone level and waist circumference.

was significantly higher in the nHPT group (34.2%, n = 28) than in the control group (23.8%, n = 19) using the Turkish WC cutoff values (Figure 4).

Discussion

In this study, we have shown that MetS components were higher in patients with nHPT. The percentage of patients meeting the MetS criteria of the NCEP ATP III was significantly greater in the nHPT group (32.9%) than in the control group (22.5%). However, using the Turkish WC cutoff values of >90 cm (women) and >100 cm (men), MetS was found in 34.1% of the nHPT group and 23.7% of the control group.

Among the major studies from Turkey examining the prevalence of MetS, a meta-analysis by Abacı et al[13] should be noted, which reviewed the results from 4 large epidemiological studies including the METSAR (Prevalence of Metabolic Syndrome among Turkish Adults) study,[14] Gundogan et al's study,[15] the CREDIT study (Chronic REnal Disease In Turkey),[16] and the KHRF study (Prevalence of Chronic Diseases and Risk Factors)[17] conducted by the Turkish Ministry of Health. The meta-analysis showed that the MetS prevalence was 32.9% for the entire population, 38.3% for females, and 26.8% for males.[13] Interestingly, the overall MetS prevalence reported in that meta-analysis is identical to the MetS prevalence of 32.9% that we found in patients with nHPT using the ATP III criteria.[13] Another study from Turkey, the Heart Disease and Risk Factors in Turkish Adults (TEKHARF) study, reported MetS prevalence rates of 28% among males and 40% among females.[18]

While the MetS prevalence of the nHPT group found in the present study is similar to the Turkish MetS prevalence, control group showed a lower prevalence than the Turkish prevalence. However, it is noteworthy that the MetS prevalence was higher in the nHPT group compared to control group. In this study, we included a group of patients diagnosed with nHPT who are followed by our team. Randomly selected, age- and sex-matched patients were included as a control group. In order to avoid bias, we did not take into account

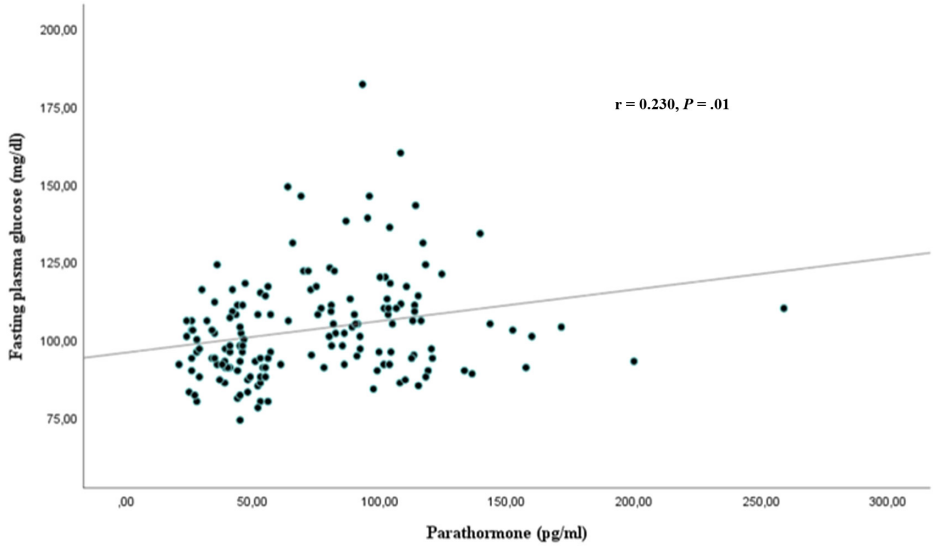

Figure 2. Correlation between parathormone level and fasting plasma glucose.

Table 3. Comparison of Individuals Meeting the NCEP-ATP III MetS Diagnostic Criteria Between nHPT and Control Groups

		nHPT (n = 82)		Control (n = 80)		
		n	%	n	%	P
WC, F > 88 cm, M > 102 cm	Yes	69	84.1	56	70.0	***.032***
	No	13	15.9	24	30.0	
TG > 150 mg/dL	Yes	36	43.9	25	31.3	.097
	No	46	56.1	55	68.8	
HDL-C, F < 50 mg/dL, M < 40 mg/dL	Yes	26	31.7	24	30	.721
	No	56	68.3	56	70	
BP > 130/85 mm Hg	Yes	24	29.3	21	26.3	.668
	No	58	70.7	59	73.8	
FPG > 110 mg/dL	Yes	30	36.6	18	22.5	***<.001***
	No	52	63.4	62	77.5	

BP, blood pressure; F, females; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; M, males; MetS, metabolic syndrome; nHPT, normocalcemic hyperparathyroidism; TG, triglyceride; WC, waist circumference.

the anthropometric measurements, blood pressure values, and laboratory test results of control subjects; thus, we were blinded to the patient data. Although our control group did not differ significantly from the nHPT group in terms of body weight and height, BMI was greater (overweight) in the nHPT group. Considering that this could confound our laboratory test results, an ANCOVA adjusted for BMI was conducted. After adjustment for BMI, significantly greater WC, WHR, FPG, total-C, and LDL-C values were observed in the nHPT group compared to control group. Higher TG levels were found in the nHPT group (non-significant difference vs. controls), but HDL-C levels were comparable between the groups. This suggests that nHPT patients are likely to have an unfavorable metabolic profile not only because of higher BMI but also due to elevated FPG and cholesterol levels.

The selection of the control group retrospectively can be considered as a limitation. However, in a prospective study by Yener-Ozturk et al[4]

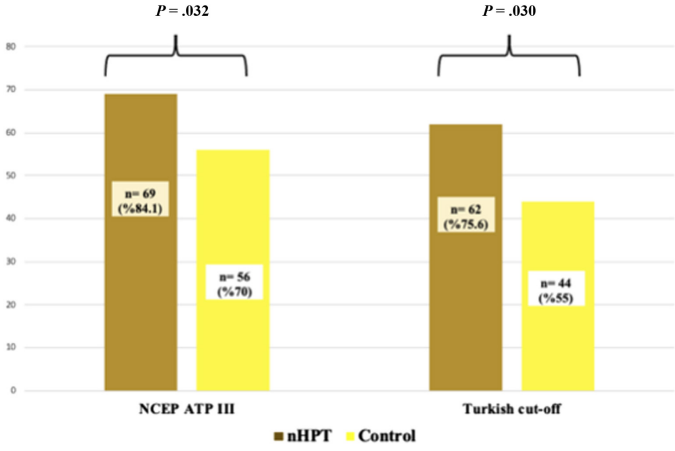

Figure 3. Numbers and percentages of individuals with increased waist circumference in nHPT and control groups. *Using the WC cutoff values reported in Turkish Endocrinology and Metabolism Society (TEMD) guidelines[12] for the Turkish population (right). WC, waist circumference.

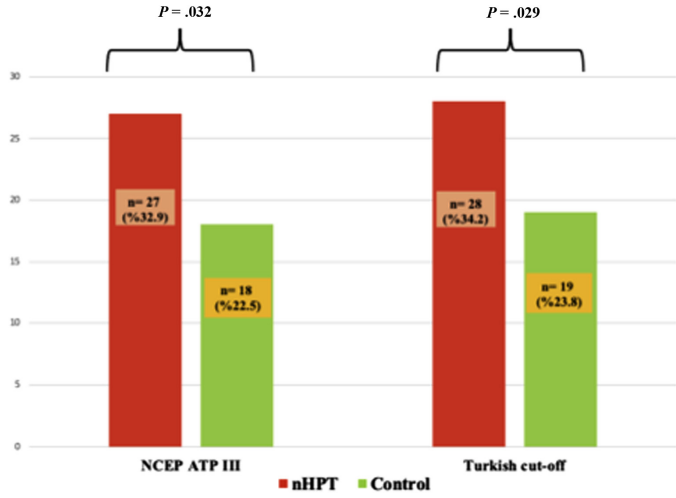

Figure 4. Numbers and percentages of individuals with MetS in nHPT and control groups. *The MetS presence was identified using the WC cutoff values adopted by the NCEP ATP III for the NCEP ATP III group (left) and using the Turkish population-specific WC cutoff values from Ref. 12 (right). MetS, metabolic syndrome; WC, waist circumference; NCEP ATP III, National Cholesterol Education Program Adult Treatment Panel III.

mean BMI values were 31.5 kg/m^2 (classified as obese) in the nHPT group and 29.5 kg/m^2 (classified as overweight) in the control group, which are consistent with our findings. Thus, the similarity of our control group to that of the aforementioned prospective study suggests that our retrospectively randomized control group represents the general population in Turkey. In addition, in a retrospective study by Hagström et al[3] both pHPT and nHPT groups had a greater mean BMI compared to control group, which is in line with our results. Taken together, these data suggest that nHPT patients tend to have a high BMI.

In our study, patients with nHPT showed greater BMI, WC, and WHR than the control subjects. Since the numerator in the WHR is WC, increased WHR due to increased WC was an expected finding for patients with nHPT. In the study by Yener-Ozturk et al[4] although BMI values were similar in patient and control groups, mean WC values of nHPT and pHPT patients were significantly greater than that of control group. The higher mean WC values in nHPT patients than in the control group as observed in our study is consistent with Yener-Ozturk et al's[4] results. In a Swedish cohort study by Ahlström et al[19] in 70-year-old individuals, PTH level was positively correlated with BMI and WC in the pHPT group. Similarly, a positive correlation was found between PTH and WC in our study, but BMI was not correlated with PTH.

In the METSAR study by Kozan et al[14] hypertension and abdominal obesity were the most common components found among individuals with MetS. In that study, overall frequency of abdominal obesity was 36.2% (17.2% in males and 54.8% in females). Likewise, abdominal obesity was the most common MetS component in our study. When we used both NCEP ATP III and Turkish population-specific WC cutoff values, the frequency of increased WC was higher in the nHPT group than in the control group. Moreover, the prevalence of abdominal obesity in both nHPT and control groups was higher than that of the Turkish population.

In the prevalence studies from Turkey, adult population over the age of 18 (mostly 20 years of age) was screened,[10,11,14-18] whereas our study subjects were in their 50s. This may explain the higher abdominal obesity prevalence in our study compared to the reported abdominal obesity prevalence in Turkey.

Similarly, the TEKHARF study found that the prevalence of abdominal obesity and MetS increases with age and reported abdominal obesity prevalence figures of 64.3% for males and 78.7% for females.[18] Additionally, in the same study, it was observed that BMI and WC tend to increase until the fifth decade of life (50-59 years of age) and decrease thereafter.[18] Considering that the majority of our study subjects were females and nHPT patients and controls were aged 50 years or older, the abdominal obesity prevalence rates (84% for patients and 70% for control subjects) found using the ATP III WC cutoff values indicate a higher WC in the nHPT group compared to control group and the Turkish female population in this age group.

Abdominal obesity characterized by increased WC is the major component of MetS. Increased insulin resistance and impaired glucose metabolism occur in the background of abdominal obesity. Since our study had a retrospective design and serum insulin level is not measured routinely at our outpatient clinic, Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) data were not available, and therefore, it is not possible for us to comment on insulin resistance. However, the patient group showed higher mean FPG levels compared to the control group. The mean FPG level was found to be significantly higher in the nHPT group after adjustment for BMI. In our study, 30% of the nHPT patients and 22.5% of the control subjects had an FPG above 110 mg/dL. In addition, a positive correlation was observed between PTH level and FPG, suggesting that increased PTH is associated with elevated FPG. Mixed results were reported for FPG by studies in patients with nHPT. Hagström et al[3] showed that although FPG concentrations were significantly higher in nHPT patients compared to controls, they were still within the normal reference range. In Yener-Ozturk et al's[4] study, while increased FPG level and higher prevalence of impaired oral glucose tolerance test (OGTT) and type 2 diabetes mellitus (DM) were found in nHPT and pHPT patients than the control group, HOMA-IR index and HbA1c levels were comparable.[4] In our study, there were no individuals diagnosed with DM among nHPT patients and control subjects. For this reason, a comparison for HbA1c could not be made. In former studies, it was reported that baseline measurements of FPG, glucose responses to OGTT, and HOMA-IR levels did not differ between nHPT population and control group, and no deterioration of glucose metabolism was observed at follow-up 4 years later. However, the number of nHPT patients was very small in these studies.[20,21] In 2 other studies, the prevalence of impaired fasting glucose (IFG) was similar between pHPT patients and nHPT patients.[22,23] The heterogeneity of these findings may be due to the use of different parameters such as FPG, IFG, HOMA-IR, or glycated haemoglobin (HbA1c) to investigate glucose metabolism abnormalities.

We also compared the study groups with respect to another component of MetS, namely, systolic and diastolic blood pressures, which are frequently used to estimate cardiovascular risk scores. After adjusting for BMI on ANCOVA, no significant difference was observed between the groups despite greater systolic and diastolic BP values in the nHPT group. In the current study, 29.3% of nHPT patients and 26.3% of controls had a BP above 130/85 mmHg. The PatenT (Prevalence, Awareness, Treatment and Control of hypertension in Turkey) study reported a hypertension prevalence of 31.8% in the Turkish population.[24] Accordingly, it can be said that the nHPT group did not have an increased frequency of hypertension (HT), since the HT prevalence was similar to that of the Turkish population. However, the prevalence of HT among control subjects is slightly lower than the Turkish HT prevalence. This may be related to the fact that sCa levels within normal range and slightly increased PTH levels were not large enough to cause HT or that the BP measurement records were not standardized.

In the present study, nHPT group showed higher mean TC and LDL-C levels than the control group but mean TG and HDL-C levels were similar. In the study by Hagström et al[3], patients with nHPT showed increased TC, LDL, and TG levels and decreased HDL-C than the control group. These results are consistent with ours, except for TG and HDL-C findings.

A number of limitations should be noted for the current study. The retrospective design of the study is a major limitation. The patient group consisted of a limited number of nHPT patients followed at our clinic and the control group was retrospectively selected among age- and sex-matched individuals. This might seem questionable. However, as mentioned earlier, our control group had similar characteristics to control groups included in previous prospective and retrospective studies. Another limitation of our study is that the parameters which are known to be subject to measurement bias such as WC, WHR, and blood pressure were evaluated retrospectively. However, this limitation applies to both patient and control groups.

Our findings are remarkable in the sense that they showed that nHPT patients are more likely to have MetS risk factors compared to control group. One of the unique aspects of our study is that all comparisons were made using the Turkish WC cutoff values, unlike most of other Turkish studies on CVD risk factors and MetS which used the ATP III or IDF WC cutoff values. With the current study, we aimed to encourage the use of Turkish population-specific WC cutoff values in future studies by reporting Turkish WC cutoffs.

Conclusion

Although our patient group consisted of patients with nHPT, which is considered to pose a lower risk for CV diseases in comparison to pHPT, the prevalence of MetS was higher than the control group: 32.9% using the NCEP ATP III criteria and 34.1% using the WC cutoff values. These MetS prevalence rates are consistent with those reported by studies from Turkey and do not seem to be increased in patients with nHPT. However, the percentage of individuals fulfilling the MetS criteria was higher among nHPT patients compared to control subjects. This shows that, even in the case of nHPT, which is considered to have a milder course, the prevalence of MetS was relatively higher than in the control group. This suggests that nHPT may be a risk factor for the development of CV disease by predisposing patients to MetS. Further studies are warranted to corroborate these findings.

Ethics Committee Approval: The study was approved by the Local Ethics Committee of Tekirdağ Namık Kemal University, Faculty of Medicine (date: March 30, 2021, no: 2021.69.03.09).

Informed Consent: Since this was a retrospective study, written informed consent was not obtained from the patients.

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Declaration of Interests: The authors have no conflict of interest to declare.

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References

1. Bilezikian JP, Brandi ML, Eastell R, et al. Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the Fourth International Workshop. *J Clin Endocrinol Metab*. 2014;99(10):3561-3569. [CrossRef]
2. Tordjman KM, Greenman Y, Osher E, Shenkerman G, Stern N. Characterization of normocalcemic primary hyperparathyroidism. *Am J Med*. 2004;117(11):861-863. [CrossRef]
3. Hagström E, Lundgren E, Rastad J, Hellman P. Metabolic abnormalities in patients with normocalcemic hyperparathyroidism detected at a population- based screening. *Eur J Endocrinol*. 2006;155(1):33-39. [CrossRef]
4. Yener Ozturk F, Erol S, Canat MM, et al. Patients with normocalcemic primary hyperparathyroidism may have similar metabolic profile as hypercalcemic patients. *Endocr J*. 2016;63(2):111-118. [CrossRef]
5. Ayturk S, Gursoy A, Bascil Tutuncu N, Ertugrul DT, Guvener Demirag N. Changes in insulin sensitivity and glucose and bone metabolism over time in patients with asymptomatic primary hyperparathyroidism. *J Clin Endocrinol Metab*. 2006;91(11):4260-4263. [CrossRef]
6. Hill MA, Yang Y, Zhang L, et al. Insulin resistance, cardiovascular stiffening and cardiovascular disease. *Metabolism*. 2021;119:154766. [CrossRef]
7. Cornier MA, Dabelea D, Hernandez TL, et al. The metabolic syndrome. *Endocr Rev*. 2008;29(7):777-822. [CrossRef]
8. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment Panel III). *JAMA*. 2001;285(19):2486-2497. [CrossRef]
9. Zimmet P, Alberti G, Kaufman F, et al. The metabolic syndrome in children and adolescents. *Lancet*. 2007;369(9579):2059-2061. [CrossRef]
10. Satman I, Omer B, Tutuncu Y, et al. Twelve-year trends in the prevalence and risk factors of diabetes and prediabetes in Turkish adults. *Eur J Epidemiol*. 2013;28(2):169-180. [CrossRef]
11. Sonmez A, Bayram F, Barcin C, Ozsan M, Kaya A, Gedik V. Waist circumference cutoff points to predict obesity, metabolic syndrome, and cardiovascular risk in Turkish adults. *Int J Endocrinol*. 2013;2013:767202. [CrossRef]
12. Türkiye Endokrinoloji ve Metabolizma Derneği (TEMD). Obezite tanı ve tedavi Kılavuzu. 2019;21:25. Available at: https://file.temd.org.tr/Uploads/publications/guides/documents/20190506163904-2019tbl_kilavuz5ccdcb9e5d.pdf?a=1.
13. Abacı A, Kılıçkap M, Göksülük H, et al. Data on prevalence of metabolic syndrome in Turkey: systematic review, meta-analysis and meta-regression of epidemiological studies on cardiovascular risk factors. *Turk Kardiyol Dern Ars*. 2018;46(7):591-601. [CrossRef]
14. Kozan O, Oğuz A, Abacı A, et al. Prevalence of the metabolic syndrome among Turkish adults. *Eur J Clin Nutr*. 2007;61(4):548-553. [CrossRef]
15. Gundogan K, Bayram F, Gedik V, et al. Metabolic syndrome prevalence according to ATP III and IDF criteria and related factors in Turkish adults. *Arch Med Sci*. 2013;9(2):243-253. [CrossRef]
16. Süleymanlar G, Utaş C, Arinsoy T, et al. A population-based survey of Chronic REnal Disease in Turkey--the CREDIT study. *Nephrol Dial Transplant*. 2011;26(6):1862-1871. [CrossRef]
17. Bakanlığı S. *Türkiye Kronik Hastalıklar ve risk Faktörleri Sıklığı çalışması*. Yayın No: 909. Ankara; 2013. Available at: https://sbu.saglik.gov.tr/ekutuphane/kitaplar/khrfat.
18. Onat A. *TEKHARF 2017*. İstanbul: Logos Yayıncılık; 2017, 1, 3-8. Available at: http://file.tkd.org.tr/PDFs/TEKHARF-2017.pdf.
19. Ahlström T, Hagström E, Larsson A, Rudberg C, Lind L, Hellman P. Correlation between plasma calcium, parathyroid hormone (PTH) and the metabolic syndrome (MetS) in a community-based cohort of men and women. *Clin Endocrinol (Oxf)*. 2009;71(5):673-678. [CrossRef]
20. Cakir I, Unluhizarci K, Tanriverdi F, Elbuken G, Karaca Z, Kelestimur F. Investigation of insulin resistance in patients with normocalcemic primary hyperparathyroidism. *Endocrine*. 2012;42(2):419-422. [CrossRef]
21. Diri H, Unluhizarci K, Kelestimur F. Investigation of glucose intolerance in patients with normocalcemic primary hyperparathyroidism: 4-year follow-up. *Endocrine*. 2014;47(3):971-972. [CrossRef]
22. Tordjman KM, Yaron M, Izkhakov E, et al. Cardiovascular risk factors and arterial rigidity are similar in asymptomatic normocalcemic and hypercalcemic primary hyperparathyroidism. *Eur J Endocrinol*. 2010;162(5):925-933. [CrossRef]
23. Tuna MM, Çalışkan M, Ünal M, et al. Normocalcemic hyperparathyroidism is associated with complications similar to those of hypercalcemic hyperparathyroidism. *J Bone Miner Metab*. 2016;34(3):331-335. [CrossRef]
24. Türk Hipertansiyon ve böbrek Hastalıkları Derneği. *Türk Hipertansiyon Prevalans Çalışması PatenT2*. 2012. Available at: http://turkhipertansiyon.org/prevelans_calismasi_2.php.