Journal of Clinical & Translational Endocrinology 19 (2020) 100213

Contents lists available at ScienceDirect

Journal of Clinical & Translational Endocrinology

journal homepage: www.elsevier.com/locate/jcte

Parathyroid gland weight is associated with high density lipoprotein levels in patients with primary hyperparathyroidism

Aseel Al Dayyeni[a,b], Amar Mahdi[c], Yuling He[a], Stanley Z. Trooskin[b], Lingqiong Meng[a], Xiangbing Wang[a,*]

[a] Divisions of Endocrinology, Departments of Medicine, Rutgers University-Robert Wood Johnson Medical School, New Brunswick, NJ, United States
[b] Divisions of General Surgery, Departments of Surgery, Rutgers University-Robert Wood Johnson Medical School, New Brunswick, NJ, United States
[c] Program in Physiology and Integrative Biology, Graduate School of Biomedical Sciences, Rutgers, The State University of New Jersey, Piscataway, NJ, United States

ARTICLE INFO

Keywords:
Primary hyperparathyroidism
Parathyroid gland weight
High density lipoprotein (HDL)
Parathyroid hormone
Calcium

ABSTRACT

Objective: To investigate the relationship between parathyroid gland weight and high-density lipoprotein (HDL) levels in patients with primary hyperparathyroidism (PHPT).

Methods: In this retrospective case control study, we reviewed 329 PHPT patients aged from 20 to 85 years who had a parathyroidectomy at Robert Wood Johnson University Hospital. The patients were divided into 5 quintiles according to their parathyroid gland weight: 68 patients had a parathyroid gland weight < 0.3 g, 66 patients had a gland weight 0.3–0.45 g, 67 patients had a gland weight 0.45–0.7 g, 63 patients had a gland weight 0.7–1.25 g, and 65 patients had a gland weight ≥ 1.25 g.

Results: Body Mass Index (BMI) trended to be higher across the quintiles of parathyroid gland weight ($P = 0.003$). Serum calcium and PTH levels were significantly increased across parathyroid gland quintiles ($p < 0.0001$). HDL levels tended to be lower across the increasing quintiles of parathyroid gland weight ($P = 0.01$). There was a negative relationship between log parathyroid gland weight and HDL in patients with PHPT in a simple linear regression ($r = -0.160$, $P = 0.003$). The negative association remained significant after adjustment for age and BMI ($r = -0.114$, $P = 0.039$). Furthermore, parathyroid gland weight was significantly associated with levels of triglyceride ($r = 0.126$, $P = 0.02$), but this relationship lost its significance after adjustment for age and BMI ($r = 0.082$, $P > 0.05$).

Conclusions: PHPT patients with heavier parathyroid glands tended to have higher BMI and lower HDL levels.

Introduction

Primary hyperparathyroidism (PHPT) has been becoming a more recognized endocrine disease with the development of multichannel chemistry screening tests. PHPT is characterized by elevated plasma calcium levels with elevated or inappropriately normal serum concentration of intact parathyroid hormone (iPTH). The most common cause of PHPT is a single parathyroid adenoma [1], and adenoma weight is a major determinant of disease severity and clinical presentation.

Recent studies have suggested that even asymptomatic PHPT may not truly be asymptomatic and may in fact be associated with higher risk factors of cardiovascular disorders [2,3]. Previous studies indicated that increased PTH levels were associated with a higher prevalence of metabolic syndrome and obesity [4–6]. A different study showed that metabolic syndrome was involved in the cardiovascular risk associated to PHPT [7]. A population-based study, which included 87 post-menopausal women followed for 5 years, showed that low high-density lipoprotein (HDL) occurred in mild PHPT and surgery was effective in reversing the dyslipidemia [8], and our previous study showed that iPTH levels were negatively associated with HDL levels [9]. However, no association of PTH with HDL was found in the NHANES population [4]. The discrepancies among different studies may be due to the fluctuations of iPTH levels in PHPT patients. Since parathyroid gland weight may better reflect average levels of iPTH levels over time [10], we therefore investigate the association of parathyroid gland weight and HDL levels in PHPT patients treated with parathyroidectomy.

* Corresponding author at: Division of Endocrinology, Metabolism and Nutrition, Department of Medicine, Robert Wood Johnson Medical School (RWJMS), Rutgers University, Room 384, New Brunswick, NJ, United States.
E-mail address: wangx9@rwjms.rutgers.edu (X. Wang).

https://doi.org/10.1016/j.jcte.2019.100213
Received 25 October 2019; Received in revised form 20 November 2019; Accepted 21 November 2019

Subjects and methods

Patients

We reviewed the EMR records of 329 PHPT patients with single parathyroid gland adenoma or hyperplasia aged from 20 to 85-year-old who had parathyroidectomy at Robert Wood Johnson University Hospital from January 2003 to April 2016. The diagnosis of PHPT was based on standard clinical criteria: 1) confirmed hypercalcemia (calcium > 10.6 mg/dl, or ionized calcium > 5.4 mg/dL), and elevated plasma intact PTH (> 65 pg /mL); 2) 24-hour urine calcium levels > 100 mg/dL; 3) pathology confirmed parathyroid adenoma or parathyroid hyperplasia. Patients were excluded if they had multiple endocrine neoplasia, multiple gland disease or parathyroid cancer. Each patient chart was retrospectively reviewed: age, Body Mass Index (BMI = kg/m^2.), serum calcium, albumin, iPTH, 25-hydroxyvitamin D (25(OH)D), total cholesterol, HDL, Low Density Lipoprotein (LDL), Triglyceride (TG) levels, blood urea nitrogen (BUN), and 24-hour urinary calcium excretion. The indications for parathyroidectomy included symptomatic PHPT or asymptomatic PHPT with one or more criteria (patient's serum calcium level, bone mineral density (BMD), the risk of a fragility fracture, kidney stone or a reduction in creatinine clearance) for surgery as defined by the National Institute of Health guidelines [11]. The resected parathyroid gland was weighed and recorded in grams. We divided the patients arbitrarily 5 quintiles according to their parathyroid gland weight.

Laboratory analysis and procedures

Total serum calcium (mg/dL), iPTH (pg/mL), serum creatinine, serum albumin and fasting blood glucose (mg/dL) were measured by Cobas e analyzers using standard enzymatic and colorimetric assays protocol. Serum 25(OH)D (ng/mL) levels were assessed using Cobas automated radioimmunoassay analyzers. The lipid parameter including total cholesterol, HDL-cholesterol and triglyceride were assessed via Cobas e analyzer using calorimetric and enzymatic methods. LDL-cholesterol levels were calculated mathematically using the Friedewald formula: LDL = Total cholesterol - HDL - (TG/5). 24-hour urinary calcium was performed at the local laboratories.

Statistical analysis

Data were analyzed using Minitab.MPJ 16.0 and results were express as Mean ± SD. Patient characteristics were compared by quintiles of parathyroid gland weight using one-way ANOVA and Kruskal-Wallis one-way ANOVA for continuous variables. Correlations confidences and linear regression were used for assess relationship. Multivariate regression models were fit to analyze the relationship between parathyroid gland weight, PTH, vitamin D, and serum calcium levels with other relevant variables after adjustment for possible confounding factors including age and BMI. PTH, parathyroid gland weight and several other variables were positively skewed and therefore log transformed or categorized depending on the type of analysis conducted. Untransformed mean was conducted throughout for ease of interpretation. Two-sided P value < 0.05 was selected as the level of significance.

Results

The trends for the biochemical indices of disease severity across parathyroid gland weight quintiles in PHPT

Three hundred and twenty-nine PHPT patients with single gland disease has been included in this study. The five groups were quintiles by parathyroid gland weight (Table 1). There was no age difference among the groups (P = 0.5). Serum calcium and iPTH were higher across the increasing quintiles of parathyroid gland weight (P_{trend} < 0.0001, Table 1). HDL and 25(OH)D levels tended to be lower across the increasing quintiles of parathyroid gland weight (P_{trend} = 0.05–0.01). BMI was trend to be higher across the quintiles of parathyroid gland weight (P_{trend} = 0.003, Table 1). Total cholesterol, LDL, triglyceride, albumin and 24-hour urine calcium levels were similar across the parathyroid gland weight quintiles (P > 0.05, Table 1).

Parathyroid gland weight and various indices of the disease severity in PHPT patients

In a univariate regression analysis, log parathyroid gland weight was positively correlated to log iPTH, log calcium levels and 24-hour urine calcium, and adjustment for confounding factors did not change the results (P_{trend} = 0.047 to < 0.0001, Table 2). The log parathyroid gland weight was negatively associated with HDL levels before (r = −0.160, P_{trend} = 0.003) and after adjustment for age and BMI (^{r}p = −0.114, P_{trend} = 0.039, Table 2). The parathyroid gland weight was negatively associated with 25(OH)D levels before and after adjustment for age and BMI (P_{trend} ≤ 0.003). The triglyceride levels were positively associated with parathyroid gland weight (r = 0.126, P_{trend} = 0.02, Table 2), but lost its significance after being adjusted for age and BMI (^{r}p = 0.082, P_{trend} > 0.05, Table 2). There was no association among log parathyroid gland weight, total cholesterol and LDL-cholesterol (P > 0.05).

Discussion

We found that HDL tended to be lower as parathyroid gland weight increased and HDL was inversely related to parathyroid gland weight after adjustment for age and BMI. Our previous study showed that PTH level is negatively associated with HDL levels [9]. Jorde et al. showed that serum calcium levels were negatively associated with HDL-cholesterol in both men and in women, while its association with triglyceride was observed only in men [12]. So we suggest that the negative association of parathyroid gland weight on HDL may be through the effects of chronic elevated iPTH or calcium levels. In addition, our data demonstrated that serum calcium and PTH levels were significantly increased across the increasing quintiles of parathyroid gland weight. Our results also showed that log parathyroid gland weight was positively correlated to log iPTH and log calcium levels. Thus, our results support the concept that adenoma weight is one of the major determinations of PHPT disease severity.

In addition, parathyroid gland weight was also negatively associated with 25(OH)D levels, which is consistent with a previous report by Rao et al [13]. We suggest that the parathyroid gland weight maybe is the better reflection of average 25(OH)D and PTH levels over time, because individual 25(OH)D and PTH levels fluctuate depending on calcium and vitamin D intake, seasonal variation, vitamin D binding protein and other factors [14].

Our data also found that there was a trend of increasing BMI across increasing parathyroid adenoma weight. Moosgaard et al. showed that BMI was positively associated with parathyroid adenoma weight [15]. One possible explanation is that obese people have a higher fat deposition in the parathyroid gland leading to a larger tumor, but a previous study showed that there was no difference in fat content of the parathyroid gland between severely obese and lean patients [16]. Our current study showed parathyroid gland weight was correlated with serum calcium and PTH levels indicating a functional relationship [17], and obese subjects had high iPTH and monocyte chemoattractant protein-1(MCP-1) levels [5]. Furthermore, high insulin-like growth factor-1 (IGF-1) levels have been found in obese people, and Tanaka et al. have suggested that IGF-1 and IGF-2 might have a mutagenic effect on parathyroid gland growth [18,19].

Our results have potential clinical applications and support that

Table 1
Comparison of clinical characteristics and biochemical findings among groups of surgically treated PHPT patients.

Parameter	Group 1 n = 68	Group 2 n = 66	Group 3 n = 67	Group 4 n = 63	Group 5 n = 65	P- value
Age (years)	57 ± 12.4	59 ± 10.08	60 ± 13.16	59.2 ± 10.48	56.9 ± 12.5	0.5
BMI (kg/m^2)	29.04 ± 5.96	28.6 ± 6.1	29.7 ± 6.7	29.6 ± 6.04	33.0 ± 9.3	0.003
Serum Ca (mg/dl)	10.84 ± 0.44	10.85 ± 0.47	10.89 ± 0.6	11.01 ± 0.57	11.37 ± 0.9	< 0.0001
iPTH (pg/ml)	102.9 ± 43.94	102.7 ± 39.6	136.8 ± 59.8	143.9 ± 90.38	213.4 ± 138	< 0.0001
Albumin (g/dl)	4.3 ± 0.28	4.42 ± 0.23	4.2 ± 0.33	4.32 ± 0.32	4.2 ± 0.33	0.3
25-OHD (ng/ml)	32.19 ± 13.56	29.82 ± 10.7	28.35 ± 12.05	27.24 ± 8.92	25.6 ± 14.51	0.05
U-Ca (mg/24 h)	286.03 ± 131.1	280.49 ± 144.9	325.58 ± 170.35	320.91 ± 170.9	345 ± 208.7	0.08
Glucose (mg/dl)	99.6 ± 20.1	101.1 ± 21.9	101.4 ± 19.15	103.5 ± 20.6	108.5 ± 37.6	0.3
Total cholesterol (mg/dl)	193.75 ± 37.6	189.9 ± 40.7	190.9 ± 40.21	193.1 ± 40.28	191.6 ± 40.8	0.9
HDL (mg/dl)	58.7 ± 17.94	55.42 ± 15.47	55.46 ± 16.39	52.45 ± 18.8	49.02 ± 18.5	0.01
LDL (mg/dl)	110.3 ± 35.2	107.7 ± 35.39	111.58 ± 41.4	109.7 ± 34.03	112.1 ± 34.9	0.9
Triglyceride (mg/dl)	128.9 ± 70.5	136.9 ± 68.53	135.3 ± 84.35	147.7 ± 77.3	157 ± 86.9	0.2

Group 1 (parathyroid adenoma weight < 0.3 g), group 2 (parathyroid gland weight 0.3–0.45 g), group 3 (parathyroid gland weight 0.45–0.7 g), group 4 (parathyroid gland weight 0.7–1.25 g), and group 5 (parathyroid gland weight ≥ 1.25 g).

Table 2
Simple linear and multiple regression analysis (partial correlation coefficients) of relations between parathyroid gland weight (log transformed) and various laboratory results in patients with PHPT.

Log parathyroid gland weight (mg)	Simple linear regression			Adjusted multiple regression		
	N	r	P	N	^{r}p	P
Log iPTH (pg/dL)	329	0.440	< 0.0001	329	0.434	< 0.0001
Log serum Calcium (mg/dL)	329	0.276	< 0.0001	329	0.282	< 0.0001
Log 25 (OH)D (ng/mL)	271	−0.214	0.0003	271	−0.178	0.003
Log Glucose (mg/dL)	322	0.063	> 0.05	322	0.020	> 0.05
HDL-cholesterol (mg/dL)	328	−0.160	0.003	328	−0.114	0.039
Log Triglyceride (mg/dL)	328	0.126	0.02	328	0.082	> 0.05
Log LDL-cholesterol (mg/dL)	328	0.016	> 0.05	328	0.007	> 0.05
Total cholesterol (mg/dL)	328	0.002	> 0.05	328	−0.008	> 0.05
24 h urine calcium (mg/24 hr)	282	0.146	0.013	282	0.118	0.047

Abbreviation: iPTH = intact parathyroid hormone, HDL = high density lipoprotein-cholesterol, LDL = low density lipoprotein-cholesterol. Regression analyses were adjusted for age and BMI (body mass index).

parathyroidectomy should consider as the preferred treatment of PHPT if no contraindications. Surgery resection of parathyroid adenoma may not only decrease iPTH and calcium levels, increase 25(OH)D and vitamin D binding protein levels [20], but also improve dyslipidemia [8]. The potential limitation of the current study is that it is a retrospective study. We did not exclude patients who are receiving medications for preexisting components of metabolic syndrome. The patients hadn't been followed up after parathyroidectomy. In addition, we didn't have data on sex-based differences in gland weight and HDL.

Conclusions

PHPT patients with heavier parathyroid glands tend to have higher BMI and lower HDL levels. Further studies in a larger cohort tracking long-term outcomes after surgery are warranted to confirm our current findings and explore the underlying mechanisms.

Author statement

Xiangbing Wang designed the study. Aseel AL Dayyeni and Amar Mahdi collected the data and analyzed the data. Aseel AL Dayyeni drafted the manuscript. Yuling He and Lingqiong Meng revised the manuscript. Stanley Z. Trooskin was the major operator for the patients with primary hyperparathyroidism. Xiangbing Wang contributed to the interpretation of the results and critical revision of the manuscript for important intellectual content and approved the final version of the manuscript. All authors have read and approved the final manuscript. Xiangbing Wang is the study Corresponding author.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Bilezikian JP. Primary hyperparathyroidism. J Clin Endocrinol Metab 2018;103(11):3993–4004. https://doi.org/10.1210/jc.2018-01225.
[2] Huang C, Shapses SA, Wang X. Association of plasma parathyroid hormone with metabolic syndrome and risk for cardiovascular disease. Endocr Pract 2013;19(14):712–7. https://doi.org/10.4158/EP12440.RA.
[3] Han D, Trooskin S, Wang X. Prevalence of cardiovascular risk factors in male and female patients with primary hyperparathyroidism. J Endocrinol Invest. 2012;35(6):548–52. https://doi.org/10.3275/7861.
[4] Reis JP, von Muhlen D, Miller 3rd. ER. Relation of 25-hydroxyvitamin D and parathyroid hormone levels with metabolic syndrome among US adults. Eur J Endocrinol 2008;159(1):41–8. https://doi.org/10.1530/EJE-08-0072.
[5] Sukumar D, Partridge NC, Wang X, Shapses SA. The high serum monocyte chemoattractant protein-1 in obesity is influenced by high parathyroid hormone and not adiposity. J Clin Endocrinol Metab 2011;96(6):1852–8. https://doi.org/10.1210/jc.2010-2781.
[6] Mendoza-Zubieta V, Gonzalez-Villasenor GA, Vargas-Ortega G,Gonzalez B4, Ramirez-Renteria C5, Mercado M6, et al. High prevalence of metabolic syndrome in a mestizo group of adult patients with primary hyperparathyroidism (PHPT). BMC Endocr Disord 2015;16. https://doi.org/10.1186/s12902-015-0014-5.
[7] Wareham NJ, Byrne CD, Carr C, Day NE, Boucher BJ, Hales CN. Glucose intolerance is associated with altered calcium homeostasis: a possible link between increased serum calcium concentration and cardiovascular disease mortality. Metabolism 1997;46(10):1171–7. https://doi.org/10.1016/s0026-0495(97)90212-2.
[8] Hagstrom E, Lundgren E, Lithell H, Berglund L, Ljunghall S, Hellman P, et al. Normalized dyslipidaemia after parathyroidectomy in mild primary hyperparathyroidism: population-based study over five years. Clin Endocrinol (Oxf). 2002;56(2):253–60. https://doi.org/10.1046/j.0300-0664.2001.01468.x.
[9] Al-Hraishawi H, Dellatore PJ, Cai X, Wang X. Intact parathyroid hormone levels and

primary hyperparathyroidism. Endocr Res 2017;42(3):241–5. https://doi.org/10.1080/07435800.2017.1292528.
[10] Mózes G, Curlee KJ, Rowland CM, van Heerden JA, Thompson GB, et al. The predictive value of laboratory findings in patients with primary hyperparathyroidism. J Am Coll Surg 2002;194(2):126–30. https://doi.org/10.1016/s1072-7515(01)01139-5.
[11] Bilezikian JP, Brandi ML, Eastell R, Silverberg SJ, Udelsman R, Marcocci C, et al. Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the Fourth International Workshop. J Clin Endocrinol Metab. 2014;99(10):3561–9. https://doi.org/10.1210/jc.2014-1413.
[12] Jorde R, Sundsfjord J, Fitzgerald P, Bonaa KH. Serum calcium and cardiovascular risk factors and diseases: the Tromso study. Hypertension 1999;34(3):484–90. https://doi.org/10.1161/01.hyp.34.3.484.
[13] Rao DS, Honasoge M, Divine GW, et al. Effect of vitamin D nutrition on parathyroid adenoma weight: pathogenetic and clinical implications. J Clin Endocrinol Metab 2000;85(3):1054–8. https://doi.org/10.1210/jcem.85.3.6440.
[14] Wang X, Shapses SA, Al-Hraishawi H. Free and bioavailable 25-hydroxyvitamin d levels in patients with primary hyperparathyroidism. Endocr Pract. 2017;23(1):66–71. https://doi.org/10.4158/EP161434.OR.
[15] Moosgaard B, Vestergaard P, Heickendorff L, Melsen F, Christiansen P, Mosekilde L. Plasma 25-hydroxyvitamin D and not 1,25-dihydroxyvitamin D is associated with parathyroid adenoma secretion in primary hyperparathyroidism: a cross-sectional study. Eur J Endocrinol 2006;155(2):237–44. https://doi.org/10.1111/j.1365-2265.2005.02371.x.
[16] Adam MA, Untch BR, Danko ME, et al. Severe obesity is associated with symptomatic presentation, higher parathyroid hormone levels, and increased gland weight in primary hyperparathyroidism. J Clin Endocrinol Metab 2010;95(11):4917–24. https://doi.org/10.1210/jc.2010-0666.
[17] Stern S, Mizrachi A, Strenov Y, et al. Parathyroid adenoma: a comprehensive biochemical and histological correlative study. Clin Otolaryngol 2017;42(2):381–6. https://doi.org/10.1111/coa.12761.
[18] Nam SY, Lee EJ, Kim KR, et al. Effect of obesity on total and free insulin-like growth factor (IGF)-1, and their relationship to IGF-binding protein (BP)-1, IGFBP-2, IGFBP-3, insulin, and growth hormone. Int J Obes Relat Metab Disord. 1997;21(5):355–9. https://doi.org/10.1038/sj.ijo.0800412.
[19] Tanaka R, Tsushima T, Murakami H, Shizume K, Obara T. Insulin-like growth factor I receptors and insulin-like growth factor-binding proteins in human parathyroid tumors. World J Surg 1994(4);18:635-41; discussion 641-32. https://doi.org/10.1007/bf00353784.
[20] Wang X, Meng LQ, Su C, Trooskin S, Sheng ZF, Shapses S. 25-hydroxyvitamin D and Vitamin D Binding Protein Levels in Patients with Primary Hyperparathyroidism Before and after parathyroidectomy Frontiers in Endocrinology. Section of Bone Research March 2019. https://doi.org/10.3389/fendo.2019.00171.