Leptin as a predictive marker for lymph node metastasis in patients with papillary thyroid cancer

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Background
Leptin is a neuroendocrine hormone produced from adipose tissue with many vital functions. There is a well-known association between leptin and papillary thyroid cancer (PTC). Preoperative prediction of lymph node metastasis is one of the interesting topics in PTC. This study aimed to determine whether the serum leptin peptide is a significant predictor marker for node metastasis in cases with PTC.

Patients and methods
This is a prospective comparative study which was conducted at Ain Shams University Hospitals and El-Sheikh Zayed specialized hospital between January 2021 and January 2023. Forty patients with PTC were enrolled in this study and according to postoperative histopathology, we divided them into two groups: group A, 24 cases, those with pathological negative node and group B, 16 cases, those with pathological positive node.

Results
We had no statistically significant difference in the preoperative demographics data between both groups. Postoperatively, the median serum leptin level and percentage of leptin decrease were significantly higher in in group B. Multivariate logistic regression analysis showed that preoperative serum leptin level, thyroid imaging reporting and data system, multifocality, extra thyroid extension, and size of dominant nodule were significant predictors for node metastasis. There was a significant negative correlation between leptin level and age, while there was a significant positive correlation between leptin level and lymph node metastasis.

Conclusion
Preoperative serum leptin level is considered a significant predictor marker for lymph node metastasis in PTC.

Keywords:
leptin, papillary thyroid cancer, lymph node metastasis

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Introduction

Papillary thyroid cancer (PTC) is the most common form of thyroid malignancy, accounting for about 80% of them [1]. It is well known that PTC has a strong affinity for lymph node metastasis, mainly to central neck compartment (level VI) [2]. Obesity is a major global health problem which reached epidemic levels worldwide. There is strong evidence from epidemiological data showing that obesity increases the risk for several types of cancer [3].

There is a strong link between obesity and thyroid malignancy and the well-known oncogenic action of some adipokines and their respective signaling pathways has suggested that the abnormal levels of adipokines associated with obesity may be a risk factor for these aggressive thyroid cancers [4]. Leptin is an adipose-tissue-related peptide hormone contributing to the control of food intake, energy expenditure, and other activities such as cell proliferation. It is also thought to influence the development of many other human malignancies [5].

Therefore, association of leptin level with thyroid cancer has been suggested recently. In addition, an overexpression of leptin and its obesity receptor has been reported in PTC and lymph node metastasis [6,7]. Considering these facts, we aimed in this study to evaluate the serum leptin levels in PTC, and to determine whether the serum leptin peptide is a significant predictor marker for lymph node metastasis in cases with PTC.

Patients and methods

Study design

This is a prospective comparative study which was conducted at Ain Shams University Hospitals and El-Sheikh Zayed specialized hospital between January 2021 and January 2023. An informed written consent form was signed by all patients in this study, and we had an approval from the ethics committee of General Surgery Department at Ain Shams University to conduct this study.

Eligibility criteria

This study consisted of 40 patients in whom total thyroidectomy with a complete central neck dissection had been performed for cases of PTC. The study included euthyroid patients with PTC larger than 1 cm diagnosed with fine-needle aspiration cytology (FNAC) either clinically positive or clinically negative lymph node status.

We excluded the following cases: micro-PTC, patients with distant metastasis, recurrent thyroid cancer, patients with aggressive variants of PTC (diffuse sclerosing, columnar cell, and tall cell variant) and the cases in which serum leptin level maybe affected (pregnancy, diabetes, and hyperlipidemic cases).

Preoperative work up

All patients were submitted to full medical history taking, general and local neck examination. Routine preoperative laboratory investigation beside thyroid profile and lipid profile to exclude dyslipidemia. Preoperative serum leptin level was tested by enzyme-linked immunosorbent assay kit after 12 h of fasting (normal leptin level ranges from 2.5 to 21.8 ng/ml).

Three milliliters of peripheral blood from overnight fasting patients was collected preoperatively and the samples were added to polypropylene tubes and left to clot at 37°C then centrifuged at 3000*g* (gravitational force) for 10 min and the resulting serum was kept at −20°C [7].

Ultrasound image was done for all included cases to assess the size of the nodule, vascularity, extra thyroid extension and lymph node assessment (shape, size, and hilum) with special comment on the thyroid nodule by thyroid imaging reporting and data system (TIRADS) classification. Computed tomography (CT) scan of the neck with contrast was done for cases with retrosternal extension.

FNAC was done for all included cases to diagnose PTC and pathological type, plus FNAC from suspicious lymph node to confirm positive or negative metastasis.

Operative procedures

All included cases underwent total thyroidectomy plus central lymph node dissection (CLND) either prophylactic for clinically negative lymph node or therapeutic CLND and selective lymph node dissection for clinically positive lateral lymph node.

Total thyroidectomy

Low collar neck incision was done. The upper and lower subplatysmal flaps were elevated. Then the deep investing fascia was incised at midline between two anterior jugular veins to expose the strap muscles. The strap muscles were split at midline exposing the pretracheal fascia and then the thyroid gland. Ligation of the middle thyroid vein was done. Individual ligation of superior thyroid vessels close to thyroid capsule was done. Ligation of inferior thyroid veins was done at the lower pole. Then exposure of recurrent laryngeal nerve was done at tracheoesophageal groove, then we ligated the terminal branches of the inferior thyroid artery to preserve of parathyroid gland vascularity. Then good hemostasis was done with insertion of closed suction drain before closure.

Central lymph node dissection

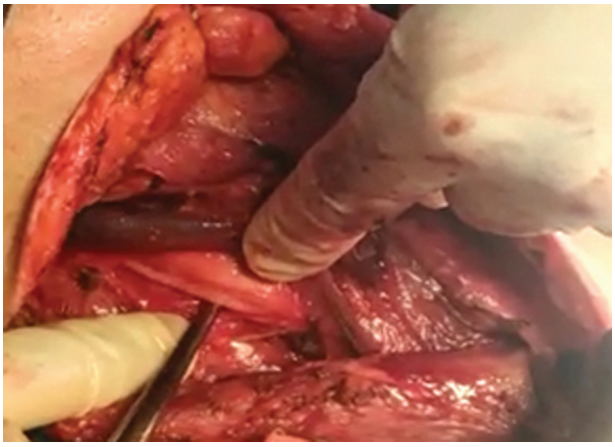
A CLND of level VI was carried. The boundaries of dissection superiorly, hyoid bone, and inferiorly the innominate artery was achieved and the lateral border of the plane of dissection was the medial border of the carotid sheath. Dissection of all fibrofatty tissue by bipolar diathermy including the pretracheal, paratracheal, and paraoesophageal lymph nodes preserving the recurrent laryngeal nerve and parathyroid glands. Then dissection of the suprasternal lymph nodes (zone VII) was done.

Selective lateral neck dissection

The collar skin incision was extended laterally to the mastoid process with elevation of upper and lower subplatysmal flaps. Then we identified the sternocleidomastoid muscle and elevated it exposing the superior belly of omohyoid muscle which was cut to expose the carotid sheath. Opening of the carotid sheath was done after preservation of ansa cervicalis nerve. Identification of internal jugular vein, common carotid artery, and vagus nerve in between was done. Dissection of all fibrofatty tissue along the internal jugular vein was done including zones II, III, and IV. After medial retraction of the sternocleidomastoid muscle to expose the posterior triangle, we identified

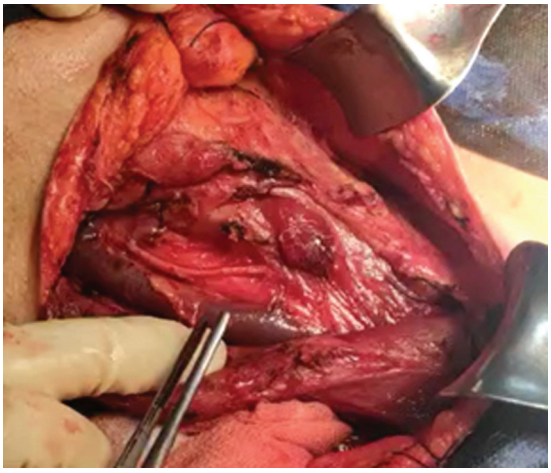
the spinal accessory nerve and phrenic nerve to preserve them and dissection of the lower half of zone V lymph nodes (below inferior belly of omohyoid muscle) was done (Figs 1 and 2).

Figure 1



Selective lateral neck dissection showing vagus nerve.

Figure 2



Selective lateral neck dissection at zones II, III, and IV.

Postoperative work up

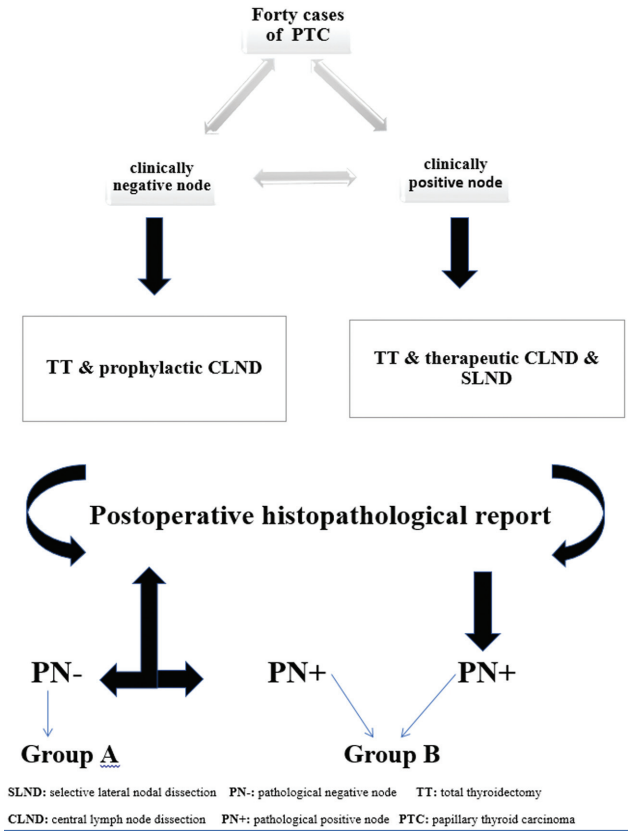
During the postoperative period, close observation for vital data was done. Proper pain control with analgesia was given. Assessment of the wound and other postthyroidectomy complications were done as bleeding, manifestation of hypocalcemia (numbness and tingling especially in face, hands and carpopedal spasm), voice change and stridor. The drain was removed if the outcome was less than 50 ml per day. We discharged the patient once vitally stable with no major postoperative complication necessitating hospital admission. Postoperative serum leptin was measured in all patients after 1 month.

According to the histopathological report for operated cases, we divided them into two groups: group A and group B:

Group A: those who were clinically negative lymph node preoperatively and after prophylactic CLND, the final histopathological report confirmed them to be pathologically negative (PN–).
Group B: those who were clinically positive lymph node preoperatively and after selective lymph node dissection, final histopathological report confirmed them to be pathologically positive (PN+) or cases who were clinically negative lymph node preoperatively and after prophylactic CLND, final histopathological report found them to be pathological positive (PN+).

Then we compared between both groups as regard preoperative data (age, sex, BMI, hypertension), operative data (operative time, bleeding, and nerve injury) and postoperative data; hospital stay, postoperative complications [hypocalcemia (symptomatic or biochemical <8 mg/dl), bleeding and voice change or stridor], and the difference in serum leptin between preoperative and postoperative level to determine if serum leptin level is a predictive marker for lymph node metastasis in PTH (Fig 3).

Figure 3



Flow chart of the study design with identification of both groups according to histopathology report.

Statistical analysis

Data management and statistical analysis were done using SPSS, version 28 (IBM, Armonk, New York, USA). Quantitative data were described as mean and SD and were compared using independent *t* test or Mann–Whitney *U* test for normally and nonnormally distributed numerical variables, respectively. Qualitative data were described as numbers and percentages and were compared using the χ^2 test. Receiver operating characteristic (ROC) analysis was used to assess the predictive power of leptin node metastasis. Area under curve with 95% confidence interval, best cut-off point, and diagnostic indices were calculated. The strength of correlation between variables were tested using Pearson correlation. Multivariate logistic regression analysis was done for predicting node metastasis. The odds ratio and the 95% confidence interval were calculated. *P* values less than 0.05 were considered significant.

Results

Forty patients with PTC diagnosed by FNAC were enrolled in this study. All patients were recruited from Ain Shams University Hospitals and Sheikh Zayed specialized hospital between January 2021 and January 2023 and according to the histopathological report for our operated cases (40 cases), we divided them into two groups: group A, 24 cases, those with pathological negative node and group B, 16 cases, those with pathological positive node.

No significant correlations were reported between both groups regarding the general characteristics of the studied patients and radiological findings except for TIRADS score which was significantly higher in group B. Preoperative serum leptin level was significantly higher in group B (Tables 1–3).

Table 1 General characteristics of the studied patients

	Group A (24 cases, PN –ve)	Group B (16 cases, PN +ve)	*P* value	Significance
Age (years) (mean±SD)	45±14	49±10	0.291*	NS
Sex [*n* (%)]				
Male	7 (29.2)	4 (25.0)	0.772**	NS
Female	17 (70.8)	12 (75.0)		
BMI (kg/m^2) (mean±SD)	28.5±4.9	29.9±3.6	0.341*	NS
HTN [*n* (%)]	4 (16.7)	2 (12.5)	0.718**	NS

HTN, hypertension; NS, nonsignificant; PN, pathological negative node; PN+, pathological positive node. *Independent *t* test. **χ^2 test.

Table 2 Preoperative serum leptin level in the studied patients

	Group A (24 cases, PN –ve)	Group B (16 cases PN +ve)	*P* value	Significance
Preoperative serum leptin ng/ml (mean±SD)	27.03±7.07	35.36±8.00	<0.001*	Significant

PN–, pathological negative node; PN+, pathological positive node. *Mann–Whitney *U* test.

Table 3 Radiological findings in the studied patients

	Group A (24 cases, PN –ve)	Group B (16 cases, PN +ve)	*P* value	Significance
TIRADS (median)	4 (2–5)	5 (4–6)	0.041*	Significant
U/S criteria [*n* (%)]				
Cystic	3 (12.5)	0	0.429**	NS
Mixed	9 (37.5)	7 (43.8)		
Solid	12 (50)	9 (56.3)		

NS, nonsignificant; PN–, pathological negative node; PN+, pathological positive node; TIRADS, thyroid imaging report and data system; US, ultrasound. *Mann–Whitney *U* test. **χ^2 test.

Table 4 Operative characteristics in the studied patients

	Group A (24 cases, PN –ve)	Group B (16 cases, PN +ve)	*P* value	Significance
Operative time (min) (mean±SD)	124.17±15.41	139.60±8.71	0.055*	NS
Intraoperative bleeding [*n* (%)]	0	1 (6.25)	0.4**	NS
RLN injury [*n* (%)]	0	1 (6.25)	0.4**	NS
Spinal accessory nerve injury [*n* (%)]	0	1 (6.25)	0.4**	NS

NS, nonsignificant; PN–, pathological negative node; PN+, pathological positive node; RLN, recurrent laryngeal nerve. *Mann–Whitney *U* test. **χ^2 test.

Table 5 Postoperative characteristics in the studied patients

	Group A (24 cases, PN –ve)	Group B (16 cases, PN+ve)	*P* value	Significance
Hospital stay (days) (mean±SD)	2.04±1.52	2.44±2.48	0.534*	NS
Voice change *n* (%)]	1 (4.17)	1 (6.25)	0.767**	NS
Hypocalcemia [*n* (%)]	5 (20.83)	6 (37.5)	0.4**	NS

NS, nonsignificant; PN–, pathological negative node; PN+, pathological positive node. *Mann–Whitney *U* test. **χ^2 test.

Table 6 Postoperative pathological findings in the studied patients

	Group A (24 cases, PN –ve)	Group B (16 cases, PN +ve)	*P* value	Significance
Size of dominant nodule (cm) (mean±SD)	1.7 (1–3.5)	3.5 (1.5–5.8)	<0.001*	Significant
Extra thyroid extension [*n* (%)]	0	10 (62.5)	<0.001**	Significant
Multifocality [*n* (%)]	4 (16.7)	9 (56.3)	0.009**	Significant

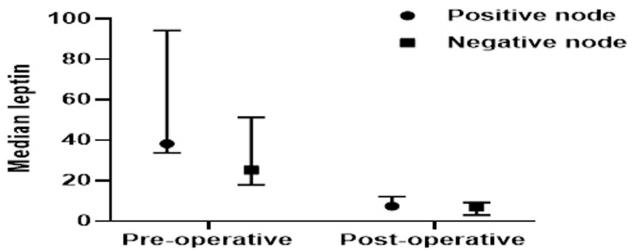
PN–, pathological negative node; PN+, pathological positive node. *Mann–Whitney *U* test. **χ^2 test.

Table 7 Postoperative serum leptin level

	Group A (24 cases, PN –ve)	Group B (16 cases, PN +ve)	*P* value	Significance
Postoperative leptin level (ng/ml) (mean±SD)	5.69±1.78	9.92±2.03	<0.001*	Significant
	3.01–7.59	7.47–12.5		
Percentage of leptin decrease (%) (mean±SD)	20.33±8.14	26.30±9.02	0.036*	Significant
	8.92–36.56	12.46–37.04		

PN–, pathological negative node; PN+, pathological positive node. *Mann–Whitney *U* test.

Figure 4



Change in leptin level.

Table 8 Multivariate logistic regression analysis for prediction of node metastasis

	OR (95% CI)	*P* value	Significance
Leptin	1.338 (1.08–1.657)	0.008	Significant
TIRADS	6.173 (1.434–26.566)	0.015	Significant
Multifocality	11.902 (1.790–79.138)	0.01	Significant
Age	1.0289 (0.976–1.084)	0.275	NS
Extra thyroid extension	6.35 (0.658–0.918)	<0.001	Significant
Size of dominant nodule	6.19 (1.75–21.84)	<0.001	Significant

CI, confidence interval; NS, nonsignificant; OR, odds ratio; TIRADS, thyroid imaging report and data system.

No significant differences were detected between group A and group B regarding operative and postoperative characteristics (Tables 4 and 5). The size of dominant nodule, extra thyroid extension and multifocality were significantly more in group B (Table 6).

Postoperatively, the median serum leptin level and percentage of leptin decrease were significantly higher in in group B (Table 7, Fig. 4).

Multivariate logistic regression analysis showed that preoperative serum leptin level, TIRADS, multifocality, extra thyroid extension, and size of dominant nodule were significant predictors for node

Table 9 Correlation between leptin level and (age, BMI, size of dominant nodule, and sex)

		Leptin level (ng/ml)
Age (years)	*r*	–0.456
	P value	0.003*
BMI (Kg/m^2)	*r*	0.073
	P value	0.654
Size of dominant nodule (cm)	r	0.137
	P value	0.398
Sex	*r*	–0.080
	P value	0.601
Extra thyroid extension	*r*	0.041
	P value	0.845
Multifocality	*r*	0.110
	P value	0.521
Positive nodal metastasis	*r*	0.333
	P value	0.045*

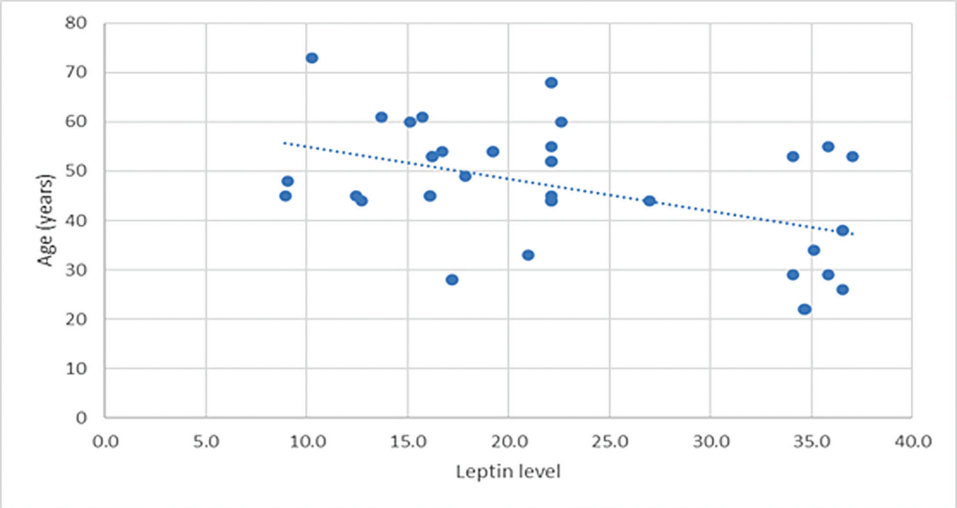
r, Pearson coefficient. *Significant as *P* value less than or equal to 0.05.

Table 10 Diagnostic accuracy of preoperative serum leptin in prediction of node metastasis

	Cut off	Sensitivity (95% CI)	Specificity (95% CI)	AUC (95% CI)	*P* value	Significance
Preoperative serum leptin (ng/ml)	>25.3	87.50	50.00	0.734	0.002	Significant

AUC, area under the curve; CI, confidence interval.

Figure 5

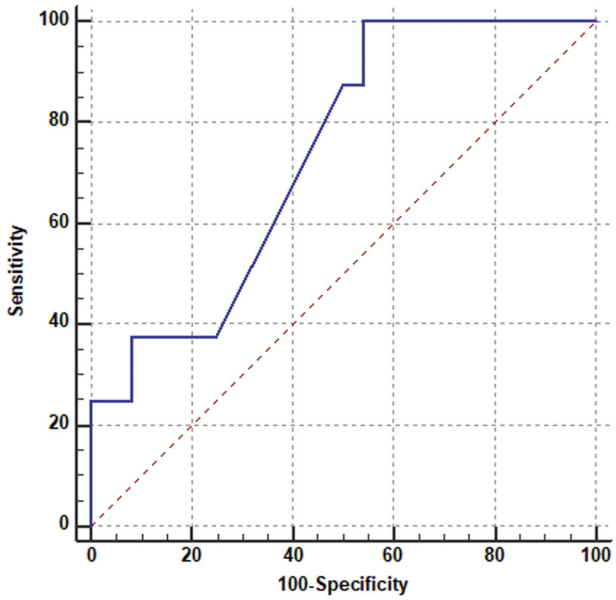


Correlation between leptin level and age of the studied groups.

metastasis, controlling for sex, and BMI, while age was insignificant predictors for node metastasis (Table 8).

There was a significant negative correlation between leptin level and age, while there was a significant positive correlation between leptin level and lymph node metastasis (Table 9 and Fig. 5).

Figure 6



Receiver operating characteristic curve of preoperative serum leptin level in prediction of node metastasis.

ROC analysis was done for using serum leptin level in prediction of nodal metastasis, it showed a significant excellent correlation (area under curve of 0.734, $P<0.001$) at cut off more than 25.3 ng/ml, with 87.5% sensitivity and 50% specificity (Table 10 and Fig. 6).

Discussion

Prophylactic CLND is one of the debatable points in the management of PTC. Prophylactic dissection involves variable intraoperative and postoperative complications especially nerve injury which may be airway threatening. On the opposite side and due to the high affinity of lymph node metastasis in PTC, there is a risk of recurrence with difficult management. So, preoperative prediction of cervical lymph node metastasis in clinically negative lymph node is beneficial [7].

The carcinogenic effect of leptin is related to many theories. It has a mitogenic effect and play a major role in oxidation process which is an important risk factor in carcinogenesis. Another theory which explains the oncogenic effects of leptin in cancer especially PTC is that it stimulates the cell proliferation and inhibits the apoptosis [4].

There are many studies which had confirmed the increased expression of leptin and its receptor in

PTC. There is a strong association between the leptin hormone levels and PTC, so it may be considered as predictor for diagnosis of PTC in suspected thyroid nodule [7].

Secondary to the previous facts, many researchers started to study the link between leptin and lymph node metastasis in PTC and if we can use it as a preoperative predictor for node metastasis.

In our study, we found a significant increase in TIRADS score in group B (pathological positive node). It is a matter of interest, although lymph node status (even being suspicious by sonographic criteria) is not within the criteria of TIRADS score but it is significantly correlated to lymph node status and this fact is proved by many studies as Zhong *et al.* [8].

In our study we did not find any significant difference in the mean operative time between both groups, and this can be explained by performing the procedures by one experienced surgical team in our 40 patients.

We did not find a significant difference between both groups in intraoperative and postoperative complications. We had accepted incidence of intraoperative and postoperative complications when compared with literature [9].

In our study, no significant difference in hospital stay was detected between both groups and this explained by the nonsignificant difference between both groups in postoperative hypocalcemia (the most common cause of postoperative hospital stay).

Regarding the leptin hormone level, the preoperative leptin and the percentage of leptin decrease were significantly higher in group B. Much research studied the relation between PTC and leptin hormone, some of them used the serum leptin level and some used the expression of leptin and its receptors in tumor cells.

Also, according to Akinci *et al.* [10] study, who compared leptin levels in 43 PTC patients versus 30 healthy female controls, they reported that serum leptin levels was higher than in PTC than control group (21.15 vs. 9.89 ng/ml) and the percentage of postoperative leptin decrease was statistically significantly higher in PTC cases.

Zhang *et al.* [11] study examined the expression of leptin and its receptor in 76 PTC, reported that leptin was expressed in the tumor cell cytoplasm in 72.4% of the cases while its receptor was expressed in 73.7% of the cases.

Our results agree with these studies and documenting that leptin hormone is considered a tumor marker related to the tumor volume (primary mass and metastasis).

In our study, multivariate logistic regression analysis done for predicting node metastasis showed that leptin, TIRADS, multifocality, extra thyroid extension and size of dominant nodule were significant predictors for node metastasis.

Akinci and colleagues study showed that leptin, TIRADS were significant predictors for node metastasis [10]. Consistently, Cheng et al. [12] study revealed that leptin is associated with increased risk of nodal metastasis.

In the current study, there was no correlation between leptin level and BMI, size of dominant nodule, extra thyroid extension, multifocality and sex. There was a significant negative correlation between leptin level and age while we found a significant positive correlation between leptin level and nodal metastasis. In this point of correlation between leptin and other factors, we found a large variation in results by reviewing the literatures.

In agreement with our results, Abostate *et al.* [13] study revealed that there was a significant correlation between age and node metastasis with preoperative serum leptin level with no correlation with BMI, sex, and multifocality. However, they had a significant correlation with tumor size and extra thyroid extension in contrast to our findings. Similarly, Holah *et al.* [14] study reported that there was no significant association between expression of leptin with size of dominant nodule and sex in the studied cases of papillary carcinoma. However, there was no correlation between leptin level and age.

Inversely, Zhang *et al.* [11] study showed that PTC cases with positive leptin staining were associated with larger tumor size but were not associated with multifocality, age or lymph node metastasis.

In Al-Hakami *et al.* [15] cohort study (including 23 PTC cases), leptin receptors expression was strongly related with age, sex, extra thyroid extension, size, node metastasis and histological type. In Cheng *et al.* [12]

study, expression of both leptin and its receptors were associated only to size and node metastasis but not associated with age, sex, multifocality, BMI and extra thyroid extension.

In Fan and Li study (including 93 PTC cases), expression of leptin and its receptors were associated with size, node metastasis, and advanced stage. The great finding in their study was that the 5 years disease survival rate was significantly less in cases with positive expression of leptin and its receptors than negative expression cases [16].

The major variation between studies in these findings may be related to small size sample in some of them, different races between these studies, besides some of them (as our study) depend on serum leptin level not expression in tumor tissue.

In our opinion, we think that the correlation between leptin and other factors is not of major clinical importance except for node metastasis (for preoperative prediction) and 5 years disease survival rate (for prognosis). Also, we think that serum leptin level (although less accurate) may be more applicable than tumor expression because it is less expensive and less operator dependent.

In the presents study, ROC analysis showed that the best cut-off value of leptin level for predicting node metastasis was 25.3 ng/ml at which sensitivity and specificity were 87.5 and 50%, respectively. Also, Holah *et al.* [14] study reported a cut-off value 27.4 ng/ml at which sensitivity and specificity were 98.7 and 66.5%, respectively for predicting node metastasis.

We have many limitations including small size sample and nonrandomized method of comparison, and we did not study the correlation between leptin and postoperative prognosis as survival rate. We need a larger sample size or meta-analysis supporting the strong correlation between leptin and node metastasis to reach the point that we can do prophylactic lymph node dissection in PTC depending on serum leptin level.

Conclusion

Preoperative serum leptin level is considered a significant predictor for lymph node metastasis in PTC.

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Nil.

Conflicts of interest

There are no conflicts of interest.

References

1 Lundgren CI, Hall P, Dickman PW, Zedenius J. Clinically significant prognostic factors for differentiated thyroid carcinoma: a population-based, nested case-control study. Cancer 2006; 106:524–531.

2 Grodski S, Cornford L, Sywak M, Sidhu S, Delbridge L. Routine level VI lymph node dissection for papillary thyroid cancer: surgical technique. ANZ J Surg 2007; 77:203–208.

3 Roberts DL, Dive C, Renehan AG. Biological mechanisms linking obesity and cancer risk: new perspectives. Annu Rev Med 2010; 61:301–316.

4 Uddin S, Hussain AR, Siraj AK, Khan OS, Bavi PP, Al-Kuraya KS. Role of leptin and its receptors in the pathogenesis of thyroid cancer. Int J Clin Exp Pathol 2011; 4:637–643.

5 Lin TC, Huang KW, Liu CW, Chang YC, Lin WM, Yang TY, Hsiao M. Leptin signaling axis specifically associates with clinical prognosis and is multifunctional in regulating cancer progression. Oncotarget 2018; 9:17210–17219.

6 Ray A, Cleary MP. The potential role of leptin in tumor invasion and metastasis. Cytokine Growth Factor Rev 2017; 38:80–97.

7 Hedayati M, Yaghmaei P, Pooyamanesh Z, Zarif Yeganeh M, Hoghooghi Rad L. Leptin: a correlated Peptide to papillary thyroid carcinoma? J Thyroid Res 2011; 2011:832163.

8 Zhong M, Zhang Z, Xiao Y, He Y, Chen Y, Huang W, Lu L. The predictive value of ACR TI-RADS classification for central lymph node metastasis of papillary thyroid carcinoma: a retrospective study. Int J Endocrinol 2022; 2022:4412725.

9 Ardito G, Revelli L, Polistena A, Lucchini R, Giustozzi E, Guidi ML, *et al.* Complications of neck dissections in papillary thyroid carcinoma: a modified procedure to reduce parathyroid morbidity. In Vivo 2016; 30:303–308.

10 Akinci M, Kosova F, Cetin B, Aslan S, Ari Z, Cetin A. Leptin levels in thyroid cancer. Asian J Surg 2009; 32:216–223.

11 Zhang GA, Hou S, Han S, Zhou J, Wang X, Cui W. Clinicopathological implications of leptin and leptin receptor expression in papillary thyroid cancer. Oncol Lett 2013; 5:797–800.

12 Cheng SP, Chi CW, Tzen CY, Yang TL, Lee JJ, Liu TP, Liu CL. Clinicopathologic significance of leptin and leptin receptor expressions in papillary thyroid carcinoma. Surgery 2010; 147:847–853.

13 Abostate A, Elmaraghy A, Farahat M, Fadl E. Serum leptin as a diagnostic indicator for papillary thyroid carcinoma. Ain Shams Journal of Surg 2022; 15:70–79.

14 Holah NS, Shaban MI, El-Goday SF. Predictive role of leptin and cyclin D1 in papillary thyroid carcinoma: an immune-histochemical study. Egypt J Pathol 2017; 37:76–81.

15 Al-Hakami HA, Alqahtani R, Alahmadi A, Almutairi D, Algarni M, Alandejani T. Thyroid nodule size and prediction of cancer: a study at tertiary care hospital in Saudi Arabia. Cureus 2020; 12:e7478.

16 Fan YL, Li XQ. Expression of leptin and its receptor in thyroid carcinoma: distinctive prognostic significance in different subtypes. Clin Endocrinol (Oxf) 2015; 83:261–267.