Serum Leptin as a Diagnostic Indicator for Papillary Thyroid Carcinoma

Ahmed Mostafa Hassanein Ibrahim Abostate, MD; Abd-Elrahman Mohmmed Elmaraghy, MD; Mahmoud Saad Farahat, MD; Ehab Mohmmed Ali Fadl, MD

General Surgery Department, Faculty of Medicine, Ain Shams University, Egypt

Background: Papillary thyroid cancer (PTC) is one of the most common cancers worldwide and is considered to be the most common endocrinal malignancy with a higher increase in its incidence every year. This rapid continuous increase in the incidence of thyroid cancer is suggested to be as a result of many factors as the newly developed and used radiological studies which can detect subclinical cases not discovered by physical examination.

Aim of the work: This study aims to evaluate the relation of level of serum leptin in papillary thyroid carcinoma and its variability to patients and tumor characteristics.

Patients and methods: In this study we measured the level of serum leptin in 20 cases of papillary thyroid carcinoma and in 20 patients with simple nodular goiter as a control group and correlated its levels with the patient characteristics as age, sex and BMI as well as the tumor characteristics and aggressiveness like tumor type, tumor size, lymph node (LN) metastasis and extrathyroidal extension.

Results: We found that the levels of serum leptin were markedly higher in the group with PTC more than the control group. There was no significant difference of serum leptin among the different pathological subtypes of PTC and the correlation between serum leptin and infiltration of the surroundings was significant. Moreover, increased levels of serum leptin were associated with a larger tumor size. These results are consistent with many studies concerned with the same issue despite being conflicting with some of other studies.

Conclusion: Serum leptin was found to have a strong association with PTC regarding the increased incidence and the aggressive behavior so it may be used in the diagnosis of PTC and prediction of the prognosis.

Key words: Serum Leptin, Diagnostic Indicator, Papillary Thyroid Carcinoma.

Introduction

Thyroid cancer is the most common endocrine malignancy and is one of the fastest growing diagnoses. It is the 16th most common cancer worldwide. About 298,000 new cases of thyroid cancer were diagnosed in 2012, with the highest incidence reported in North America and lowest in Western Africa, It is estimated that 1.2–2.6 men and 2.0–3.8 women per 100 000 individuals are affected worldwide.[1]

The incidence of thyroid cancer has tripled over the past 30 years, Because of this rising incidence, thyroid cancer is projected to be the fourth most common cancer by 2030.[2] It has been suggested that this rapid increase in the number of the newly discovered cases is due to the development and usage of imaging technologies capable of detecting a large reservoir of subclinical disease.[3] Regarding the incidence in the Arab countries a study conducted in the National cancer institute reported that the incidence of thyroid cancer are higher in Qatar, Saudi Arabia, and the United Arab Emirates than that in Egypt.[4]

Thyroid cancer is classified into four main histopathological types which are Differentiated thyroid cancer including (papillary thyroid carcinoma (PTC)) and follicular thyroid carcinoma (FTC)), medullary thyroid carcinoma (MTC), anaplastic thyroid carcinoma (ATC) and miscellaneous carcinomas (Lymphoma, Fibrosarcoma, Squamous cell carcinoma, Teratoma and Metastatic lesions). Differentiated thyroid cancer forms the vast majority of the cases (PTC about 80%, FTC 5-10%).[5]

Growing epidemiologic studies correlated the increasing risk for thyroid carcinoma with obesity. A meta-analysis of 4 studies on thyroid carcinomas found that a 5 kg/m² increase in body mass index (BMI) was strongly associated with increased incidence of thyroid carcinoma in both men and women with a relative risk of 1.33 and 1.14, respectively.[6]

Leptin, from the Greek word (leptos) meaning thin, is an adipokine which is produced and released into the circulation mainly by adipose tissue, it plays a critical role in energy expenditure and homoeostasis. Leptin as a neuroendocrine hormone has effects on the glucose metabolism, reproductive system,

immune system, sexual maturation, pituitary-adrenal axis, thyroid, and growth hormones level.[7] There are many reports concerning the effect of leptin hormone on stimulation of cell mitosis and its involvement in carcinogenic stages of breast, lung, prostate, thyroid, kidney and ovary cells. Studies have shown that leptin by increasing cell proliferation and inhibition of apoptosis is involved in creating certain types of tumors.[8]

Furthermore, it was found that overexpression of leptin and leptin receptor is associated with tumor aggressiveness and that leptin modulates cell migration of thyroid cancer cells.[9] Increased expression of leptin and its receptor in papillary thyroid cancer has been noticed. This hormone probably through its receptor and activation of the PI3K/AKT pathway plays an important role in papillary thyroid cancer pathogenesis. It seems that the oncogenic effects of leptin on papillary thyroid carcinoma cells are related to the stimulation of cell proliferation and inhibition of apoptosis.[10] Subsequently, the French E3N study including 91,909 women confirmed a significant dose-effect relationship between BMI and thyroid cancer risk.[11]

In a study on a large cohort, Obesity receptors (ObRs) and leptin were found to be overexpressed in 80.1% and 49.1% of PTC patients, respectively, and ObR expression was strongly associated with age, gender, extrathyroidal extension, tumor stage, tumor size, node metastasis and histological type.[12]

Studies revealed that PTC tumors with both leptin and ObR overexpression were more likely to develop lymph node metastasis compared with tumors with neither leptin nor ObR Expression.[13]

Aim of the work

This study aims to evaluate the relation of level of serum leptin in papillary thyroid carcinoma and its variability to patients and tumor characteristics.

Patients and methods

Type of Study

This is a prospective case-control study conducted at Ain Shams University Hospitals.

Study settings

The study was conducted in General Surgery Department, Ain shams university hospitals and General Surgery Department in El-Salam Port Said Hospital.

Study Period

The study has been conducted between October 2020 and March 2021.

Study population

- Our study has included about 40 patients.
- The study has included two groups, the first group consists of 20 cases presented with well differentiated papillary thyroid carcinoma, and the second group has included 20 person as a control group who were presented with simple nodular goiter.

Inclusion criteria

The study has included euthyroid patients with papillary thyroid carcinoma who have been diagnosed with FNAC and patients with simple nodular goiter. All patients diagnosis has been confirmed with pathology examination.

Exclusion criteria

- Patients with recurrent thyroid carcinoma (Inability to asses 1ry tumor).
- Patients on medications for dyslipidemia or Oral contraceptive pills (Due to affection of leptin level).
- Patients who have any of the following: Hyperthyrodism, hypothyroidism, diabetes mellitus (due to affection of leptin level) and hypertension (leptin increases NO production with chronic sympathetic activation).

Ethical considerations

All participants signed an informed consent after explaining to them the objective of the study and the ability of withdrawal from the study at any time without affecting their management plan.

All patients were submitted to:-

- Full medical history.
- General and local examination.
- Radiological investigations.
- Laboratory investigations.
- Cytological and histological investigations.

History taking including

Personal history: Name, age, sex, occupation, residence, marital status, menstrual history in females, special habits.

General examination

Including general look of the patient, body built, mental status, decubitus, vital signs (Pulse, blood pressure, temperature). Examination of the head, chest, abdomen and extremities was done. Length, weight and BMI (Body Mass Index) of all the patients

were recorded.

Local examination

Examination of the thyroid gland including inspection, palpation, percussion and auscultation. Examination of the thyroid swelling if it was clinically palpable and full assessment of it including site, size, shape, consistency, contour, mobility, relation to surroundings, skin attachment and fixation, retrosternal extension, pulsation and audible pruit. Then examination of all the cervical lymph nodes was done to assess if there is enlargement or tenderness. Indirect laryngoscopy was done for all the patients for assessment of vocal cords mobility.

Radiological investigations

Neck US and duplex was done for all patients for assessment of size of the gland, vascularity, LN assessment (Shape, size, hilum), with special comment on the nodules (Site, size, shape, cystic or solid, homogenous or heterogonous, hyperechoic or hypoechoic, calcification, Halo sign, infiltration of the surroundings) for assessment of thyroid imaging reporting and data systems (TIRADS) and suspicious of malignancy. CT was done for assessment of patients with huge retrosternal extension and in patients with suspicion of infiltration of the surroundings.

Cytological investigations

FNAC was done to all patients presented in the outpatient clinic. All specimens were sent postoperatively for histopthological examination.

Laboratory investigations

Full routine laboratory investigations were done including: CBC, INR, S.creatinine, liver functions for preoperative assessment and preparation. Thyroid function tests (Free T3, Free T4, TSH) were done. Preoperative blood sample was taken after fasting 12 hours for measuring of the serum leptin.

Measurement of serum leptin level

3 ml peripheral blood from overnight fasting patients was collected preoperatively. The samples were added to polypropylene tubes and left to clot at 37°c then centrifuged at 3000 xg (Gravitational force) for 10 minutes and the resulting serum was kept at -20°c.

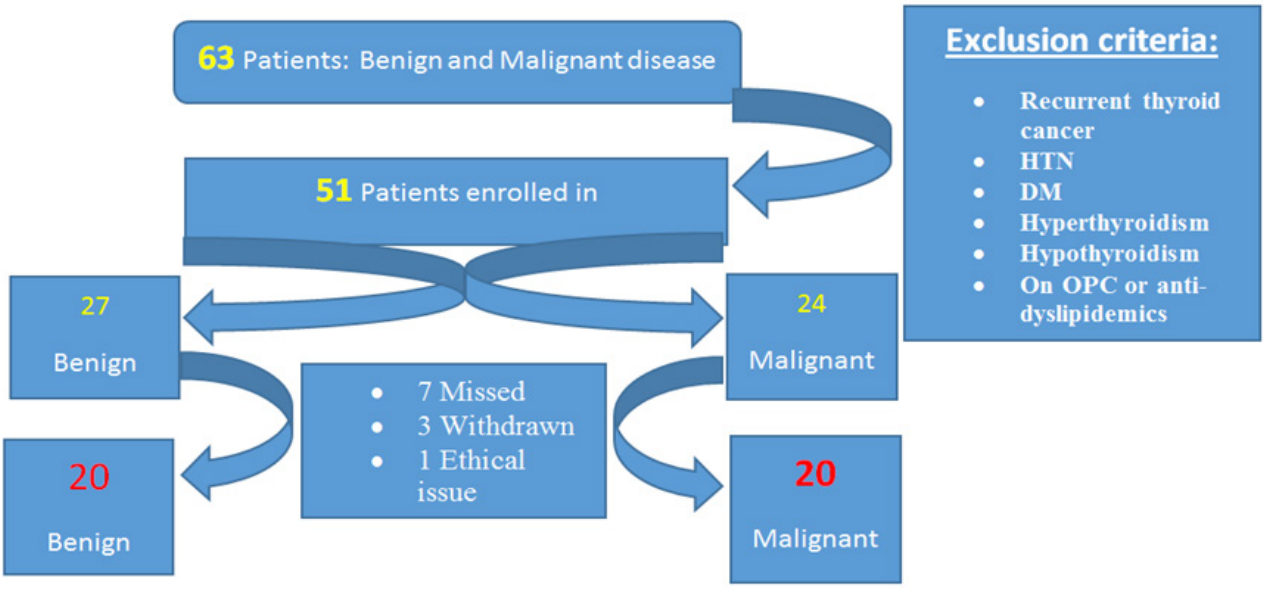


Fig 1: Patient Flowchart.

Over 8 months, 63 patients with thyroid mass have been included into our study, only 51 patients continued after applying the exclusion criteria on all patients. After clinical and radiological review of each patient and getting FNAC for them, we divided 51 patients in two group: group 1 (24 patients) who were diagnosed with PTC and group 2 (27 patients) with simple nodular goiter.

In group 1, two patients have been requested to withdraw without any reason and other two patients have not come again to follow-up in the clinic. So group 1 in the end of study was 20 patients with papillary thyroid carcinoma who diagnosed with FNAC preoperatively and confirmed with pathology examination postoperatively.

In group 2, one patient has ordered to withdraw and other one has been removed due to ethical issue. Four patients have not continued the follow-up in the clinic and one patient has been removed due to accidental discovered pathology (Papillary thyroid carcinoma). So group 2 was 20 patients with simple nodular goiter at the end of study.

Results

This case-control study included 20 patients with papillary thyroid carcinoma and 20 patient with simple nodular goiter as controls.

Table 1: Personal data in PTC group

		No. = 20
Age	Mean±SD	46.05 ± 13.36
	Range	22 – 73
Gender	Female	18 (90.0%)
	Male	2 (10.0%)
Weight	Mean±SD	79.00 ± 10.48
	Range	60 – 100
Height	Mean±SD	169.90 ± 5.67
	Range	158 – 180
BMI	Mean±SD	27.41 ± 3.82
	Range	21.26 – 37.18
BMI groups	Underweight Normal weight	0 (0.0%) 4 (20.0%)
	Overweight Obese	13 (65.0%) 3 (15.0%)

Table 2: Correlation between age/sex in both groups

		Control group	Patients group	Test value	P-value	Sig.
		No. = 20	No. = 20			
Age	Mean±SD	46.10 ± 9.40	46.05 ± 13.36	0.014•	0.989	NS
	Range	29 – 69	22 – 73			
Gender	Female	18 (90.0%)	18 (90.0%)	0.000*	1.000	NS
	Male	2 (10.0%)	2 (10.0%)			

P-value >0.05: Non significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS).
*:Chi-square test; •: Independent t-test.

Table 3: Mean BMI and BMI categories

		Control group	Patients group	Test value	P-value	Sig.
		No. = 20	No. = 20			
Weight	Mean±SD	76.50 ± 9.97	79.00 ± 10.48	-0.773•	0.444	NS
	Range	59 – 94	60 – 100			
Height	Mean±SD	163.20 ± 8.46	169.90 ± 5.67	-2.943•	0.006	HS
	Range	153– 180	158 – 180			
BMI	Mean±SD	28.71 ± 3.10	27.41 ± 3.82	1.181•	0.245	NS
	Range	23.94 – 34.02	21.26 – 37.18			
	Underweight Normal weight	0 (0.0%) 1 (5.0%)	0 (0.0%) 4 (20.0%)	2.057	0.151	NS
	Overweight Obese	11 (55.0%) 8 (40.0%)	13 (65.0%) 3 (15.0%)			

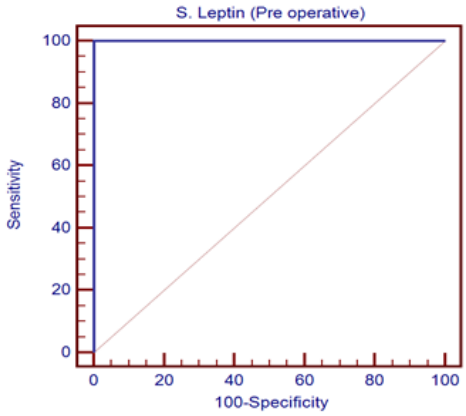
P-value >0.05: Non significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS).
*:Chi-square test; •: Independent t-test.

Table 4: Preop and postop Serum leptin level in control and patient groups

S. Leptin		Control group	Patients group	Test value•	P-value	Sig.
		No. = 20	No. = 20			
Pre operative	Mean±SD	7.42 ± 2.40	36.86 ± 17.90	-7.289	0.000	HS
	Range	3.2 – 11.2	17.93 – 77.5			
Post operative	Mean±SD	7.38 ± 2.42	6.91 ± 2.46	0.609	0.546	NS
	Range	3.2 – 11.19	3.08 – 12.2			
Mean difference		-0.04 ± 0.14	-29.95 ± 16.20	-8.257	<0.001	HS
Paired t-test		-1.426	-8.268			
P-value		0.170 (NS)	<0.001 (HS)			

P-value >0.05: Non significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS).
•: Independent t-test.

Laboratory data of patients showed that preoperative serum leptin levels ranged from 17.93 to 77.5 with a mean±SD of 36.86±17.90 and postoperative serum leptin levels ranged from 3.08 to 12.2 with a mean±SD of 6.91±2.46. Laboratory data of control group showed that preoperative serum leptin levels ranged from 3.2 to 11.2 with a mean±SD of 7.42±2.40 and postoperative serum leptin levels ranged from 3.2 to 11.19 with a mean±SD of 7.38±2.42. On comparing the serum leptin between patients and control group, there was a highly statistical significant difference (P<.01). In patient group the mean difference between preoperative and postoperative serum leptin has been 29.95 ± 16.20 which is highly significant.



Parameter	AUC	Cut of Point	Sensitivity	Specificity	PPV	NPV
S. Leptin pre operative	1.000	>11.2	100.0	100.0	100.0	100.0

Fig 2: ROC curve of S. Leptin pre operative as a predictor of patients.

Table 5: Serum leptin level correlation with Age, BMI, Tumor size in PTC group

	S. Leptin			
	Pre operative		Post operative	
	R	P-value	R	P-value
Age	0.627**	0.003	0.144	0.546
Weight	-0.023	0.925	-0.410	0.072
Height	-0.002	0.992	-0.200	0.398
BMI	-0.062	0.796	-0.312	0.180
Tumor Size	0.674**	0.001	0.334	0.150

There is a significant correlation between age and preoperative serum leptin level which is not expected. Moreover, tumor size showed a significant correlation with preoperative serum leptin.

Table 6: Correlation between Preop serum leptin and tumor charcteristics

		Pre operative		Test value	P-value	Sig.
		Range	Mean±SD			
Pathological type	Papillary microcarcinoma (4 pt)	27.06 ± 11.57	19.2 – 44.26	1.241•	0.231	NS
	Papillary thyroid carcinoma (4 pt)	39.31 ± 18.63	17.93 – 77.5			
Multifocality	No (14 pt)	32.76 ± 16.13	17.93 – 77.5	-1.630•	0.120	NS
	Yes (6 pt)	46.42 ± 19.61	19.2 – 68.4			
Extranodal extention	No (15 pt)	31.53 ± 13.03	17.93 – 63.3	-2.645•	0.016	S
	Yes (5 pt)	52.85 ± 22.42	20.38 – 77.5			
LN metastasis	No (10 pt)	26.32 ± 8.66	17.93 – 44.26	-3.218•	0.005	HS
	Yes (10 pt)	47.41 ± 18.83	23.89 – 77.5			
Tumor size groups	< 1 cm (4 Pt)	27.06 ± 11.57	19.2 – 44.26	4.168••	0.023	S
	1 - 2 cm (6 pt)	26.02 ± 7.18	17.93 – 38.2			
	2 - 4 cm (9 pt)	44.94 ± 18.57	23.8 – 77.5			
	> 4 cm (1 pt)	68.4 ± 0.0	68.4 – 68.4			
Stage	Stage 1 (11 Pt, 55.0 %)	25.30 ± 7.20	17.93 – 44.26	20.779••	0.000	HS
	Stage 2 (2 Pt, 10%)	31.15 ± 10.39	23.8 – 38.5			
	Stage 3 (4 Pt, 20%)	48.90 ± 11.03	38.2 – 63.3			
	Stage 4a (3 Pt, 15%)	67.03 ± 11.22	55.18 – 77.5			

P-value >0.05: Non significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS).
•: Independent t-test; ••: One Way ANOVA test.

Serum leptin level shows significant correlation with tumor size as tumor size more than 2cm showed noticed elevation in s. leptin level more than tumor size less than 2cm. According to tumor characteristics, both LN metastisis and extrathyroidal extension shows significant correlation with s. leptin but there is no significant between its level and multifocality. In our study staging of PTC patients range from stage 1 to stage 4a, there is a highly significant correlation between s. leptin and patient stage.

Among the 20 cases of PTC there was only 4 cases of papillary microcarcinoma (20%) while the remaining was papillary thyroid carcinoma (80%) with the ratio 1:4 with no significant difference in the level of leptin between papillary thyroid carcinoma and papillary microcarcinoma.

Table 7: Correlation between extranodal extension and tumor size and pre- and post-operative serum leptin

		Extranodal extention		Test value	P-value	Sig.
		Yes	No			
		No. = 5	No. = 15			
Tumor Size	Mean ± SD	1.88 ± 0.88	3.20 ± 1.19	-2.683•	0.015	S
	Range	0.8 – 3.5	1.4 – 4.5			
PreOP S. Leptin	Mean ± SD	31.53 ± 13.03	52.85 ± 22.42	-2.645•	0.016	S
	Range	17.93 – 63.3	20.38 – 77.5			
PostOp S. leptin	Mean ± SD	6.29 ± 2.45	8.76 ± 1.43	-2.108•	0.049	S
	Range	3.08 – 12.2	7.45 – 11.21			

P-value >0.05: Non significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS).
*:Chi-square test; •: Independent t-test.

Extrathyroidal extension shows a significant correlation with the tumor size as well as serum leptin level. Tumor size and LN metastases shows a highly significant correlation.

Table 8: Correlation between lymph node metastasis and tumor size

Tumor Size	LN metastasis		Test value	P-value	Sig.
	No	Yes			
	No. = 10	No. = 10			
Mean±SD	1.58 ± 0.85	2.84 – 0.96	-3.093•	0.006	HS
Range	0.80 – 3.50	1.40 – 4.50			
< 1 cm	4 (40.0%)	0 (0.0%)	8.444*	0.038	S
1 - 2 cm	4 (40.0%)	2 (20.0%)			
2 - 4 cm	2 (20.0%)	7 (70.0%)			
> 4 cm	0 (0.0%)	1 (10.0%)			

P-value >0.05: Non significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS) *:Chi-square test; •: Independent t-test.

Discussion

Thyroid carcinoma is the most common endocrine malignancy. It is estimated that 1.2–2.6 men and 2.0–3.8 women per 100000 individuals are affected worldwide.[14] In 2015 in the US there was about 64.300 newly diagnosed cases.[15]

Obesity is now becoming an epidemic worldwide and has been considered as a risk factor for several types of cancer.[16] Leptin serum levels are closely correlated with adiposity in humans and it is thought to be the link between obesity and cancer.[17]

In our study we found that among the 20 cases of papillary thyroid carcinoma there was 2 males (10%) and 18 females (90%) with a ratio of 1:9 and this shows that PTC was more common among females.

Kim[18] found in his study on 2057 patients that females formed 87% and males formed 13% of the patients which is nearly the same as our results. The age of the patients in his study ranged from 12 to81 with mean age (46±13). Uddin[19] found that females formed (371/512) 72,5% while males (141/512) 27.5%.

Moreover, there was no statistically significant correlation between age and leptin found by Garofalo[20] and Zhang[17] but in our study we have found significant correlation between them (P=0.003) as well as Khabaz[21] who found that leptin and obesity receptors overexpression were correlated with older age.

From these studies its obvious that thyroid cancer is more common among middle to old age people specially females.

Regarding BMI the result was slightly insignificant but generally it was lower in the group of PTC (27.41±3.82) than in the control group (28.71±3.10).

Renehan[16] conducted a large systemic review on the association of BMI and thyroid cancer risk analyzing 221 data sets and 282,137 incident cases; a 5-kg/m2 increase in BMI was strongly associated with thyroid cancer in both men (Relative risk, 1,33; P=0,02) and women (relative risk, 1,14; P=0,001).

Kitahara[22] similarly, in a pooled analysis of five prospective studies examining a total of 413,989 females and 434,953 males increasing BMI was associated with a higher risk for thyroid cancer in both men and women after adjusting for potential confounding factors. In accordance were the results of a meta-analysis by Zhao[23] the risk of thyroid cancer (TC) was significantly increased in the presence of excess body weight, either overweight or obesity.

Moreover, in a retrospective study of 2057 PTC patients it was found that higher BMI was related to a more aggressive PTC phenotype, including, increased tumor size, extrathyroidal invasion, and advanced disease stage, independently of age, sex, and other confounding factors. But no relation was found between obesity and recurrence rates. Similarly, in the study of Harari[24] assessing 443 PTC patients, Greater BMI was associated with more advanced disease stage at presentation (P=0.001) and more aggressive PTC histopathologic subtype (P=0.03). Morbidly obese patients presented more frequently with stage III or IV disease (odds ratio, 3.67; P=0.001).[25]

We found that there is no significant correlation between serum leptin level and the Body Mass Index (P=0.796) which is against the previous mentioned studies. This may be due to the small number of patients in our study.

In our study level of serum leptin was measured in both groups and it was significantly higher in the group with PTC (36.86±17.90) than the group with nodular goiter (7.42 ± 2.40) with a highly significant p value (<0.001*).

Similarly Hedayati[26] found that a significant difference was observed between the leptin hormone levels in both healthy and cancer groups. The amount of leptin hormone in cancer patients was higher than that in normal individuals, significantly (P<0.05). Furthermore, Akinci[27] reported that serum leptin levels of PTC patients were higher than in control group subjects (21.15±14.12 ng/mL vs. 9.89±0.21 ng/mL, p<0.05). The leptin levels decreased after total thyroidectomy (13.92±10.55 ng/mL) compared to pre-thyroidectomy levels (22.94±14.67 ng/mL) in 34 patients who came to the follow-up visit (p<0.05). However, the decreased post thyroidectomy levels of leptin were still statistically significantly higher than the control group levels.

Controversly, Dossus[28] showed that high adiponectin levels were associated with a lower risk of TC while leptin, and other inflammatory markers were not associated with thyroid cancer risk in both genders, only elevated IL-10 levels were associated with an increased risk of TC probably in both genders.

Leptin and Ob-R expression were observed in tumor cell cytoplasm with a positive rate of 42.2% and 57.1%, respectively, in well differentiated thyroid cancer (WDTC). There was a strong correlation of leptin expression with Ob-R expression in WDTC (r=0.636, P<0.05).[29]

Uddin[19] found high expression rates of leptin and Ob-R in PTC (49.1%, 80.1%). Moreover, Zhang[17] showed the same results according leptin and Ob-R expression (72.4%, 73.9%). Cheng[30] revealed that leptin and Ob-R were expressed in a lower rate in 36.7% and 51.0% of PTC cases, respectively. In, Yan-Lan and Xiao-Qiu study,[29] 42.2% and 57.1% of PTC samples expressed leptin and Ob-R, respectively. Despite the differences in the positive rate, all the studies proved that PTC tumors express leptin and Ob-R.

Tumor characteristics

Yan-Lan and Xiao-Qiu in their study[29] found clearly that both leptin and Ob-R were expressed in all the four subtypes of TC with statistical significance, but the leptin and Ob-R expression levels were not statistically different among PTC, FTC, MTC and ATC, which suggests that leptin or Ob-R may play an important role in the initiation stage of carcinogenesis of the four types. In this study size of the tumors ranged from 0.8 to 4.5 cm with mean size (2.21±1.09 cm).

There was a significant positive correlation between tumor size and the level of serum leptin (r=0.674, p=0.001*), and this indicates that leptin plays a main role in cell growth and proliferation thus increasing the tumor size.

The phosphatidylinositol 3 kinase (PI3K)/protein kinase B (AKT) signaling pathway is involved in the regulation of multiple cellular physiological processes by activating downstream corresponding effector molecules, which serve an important role in the cell cycle, growth and proliferation. This is a common phenomenon; overactivation of the pathway is present in human malignancies and has been implicated in cancer progression.[31] Uddin[19] reported that he investigated the oncogenic effect of leptin on PTC cells, using PTC cell lines, and this oncogenic effect is due to a combination of stimulation of cell proliferation and inhibition of apoptosis by leptin. His in vitro experiments showed clearly that leptin rapidly stimulates the PI3K pathway and induced the phosphorylation of AKT, and by activation of this key signal transduction pathway it was associated with rapid cell proliferation. In addition, prevention of leptin induced activation of PI3K with chemical inhibitors reduced significantly the activation of AKT pathway which provides a survival signal protecting cells from apoptosis.

Cheng study[30] revealed that leptin only stimulated migration of thyroid cancer cells depending on PI3K/AKT and MAPK pathways and this showed that PTC with expression of leptin receptor and/or leptin is associated with the risk of nodal metastasis. However, he found that leptin had no effect on cell growth in thyroid cancer cells and the basis for such a difference was unclear.

In this study among the 20 cases of PTC there was 5 cases with infiltration of the surroundings (25%). The lowest rate of infiltration was in the cases with papillary microcarcinoma (0%) as there was no infiltration in any of them.

Regarding the correlation between sex and aggressiveness of the tumor especially extrathyroidal extension, we noticed that it is in males (0%) and in females (27.7%), so according to sex we can not compare due to small number of patients.

Dz`epina found in his study[31] that the tumor behavior was more aggressive in males (P=0.03). Furthermore, males were more susceptible to the presence of metastatic foci (P=0.05) and more paratracheal and lateral metastasis.

In the cases with infiltration mean serum leptin and size of the tumor were higher than those in the cases with no infiltration with significant results with tumor size (0.011*). This indicates that larger tumor size at presentation and higher serum leptin all are contributing factors in the seedling and infiltration of the tumor to the surroundings.

Yan-Lan and Xiao-Qiu[29] similarly found that For PTC, leptin expression was strongly correlated with older age, larger tumour size, nodal metastasis and

advanced stage (P < 0,05). In addition, the 5-year disease-free survival (DFS) rate in patients with positive leptin or its receptor expression was lower than that in patients without expression. Moreover, Cheng[30] found in his study that papillary thyroid cancer with expression of leptin receptor and/or leptin is associated with the risk of nodal metastasis but not related to larger tumor size.

Inversely, Zhang[17] in his study demonstrated that PTC samples with positive staining for Ob-Rs (P=0.002) or leptin (P=0.016) were associated with a larger tumor size but neither leptin nor ObR expression was associated with multifocality or lymph node metastasis. In our study, multifocality showed insignificant correlation with serum leptin, in contrast LN metastasis were highly significant.

Kim[18] in a retrospective study of 2057 PTC patients, found that higher BMI was related to a more aggressive PTC phenotype regarding tumor size and infiltration of the surroundings which was independent of age, sex, and other confounding factors which is nearly to the results in our study.

Conclusion

Serum leptin was found to have a strong association with PTC regarding the increased incidence and the aggressive behavior so it may be used in the diagnosis of PTC and prediction of the prognosis.

The hope in the future is to do further studies on other types of thyroid cancer to determine if serum leptin is related to any of them or not.

Finally, we recommend conducting further studies on a larger number of patients.

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