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Association of High Serum Leptin Level with Papillary Thyroid Carcinoma: A Case-Control Study

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ABSTRACT

Background: Recently, the prevalence of thyroid cancer has increased. Although there are known risk factors for thyroid cancer, none of them can justify this recent increase. In addition to the known risk factors, other risk factors have been proposed. Leptin can be considered as one of these risk factors due to the recent increase in the prevalence of obesity in the population. Leptin is a common factor in obesity and thyroid cancer. Leptin exerts anti-apoptotic and mitogenic effects on cancer cells and also acts as an angiogenic factor. This study aimed to evaluate the serum leptin level in individuals who suffer from papillary thyroid carcinoma (PTC), cases with benign thyroid nodules (BTN), and a healthy group.

Materials and Methods: In this study, newly diagnosed patients with PTC, BTNs, as well as euthyroid healthy control subjects without nodules were included. In all these participants, various clinical and laboratory parameters including thyroid function tests and serum leptin levels were measured and compared between the three study groups. For patients with PTC, leptin was assessed 12 weeks after total thyroidectomy.

Results: Ninety-one cases with PTC, 90 cases with BTNs, and 88 controls were recruited. Serum leptin levels in the PTC group, benign group, and the control group were 22.34, 17.60, and 13.83 ng/ml, respectively, which was considerably higher in PTC cases compared to those with benign nodules and control group ($P<0.001$). There was a significant association between leptin with BMI, tumor size, and tumor stage in PTC patients. Also, in patients with BTNs, a correlation between BMI, tumor size, and leptin was observed.

Conclusion: Serum leptin levels were considerably higher in cases with PTC than those with BTNs and controls and can be considered as a potential tumor marker for papillary thyroid cancer.

Keywords: Leptin; Thyroid nodule; Thyroid Cancer, Papillary

INTRODUCTION

Thyroid cancer (TC) is a major endocrine disease worldwide, which accounts for 1.3% of all cases of cancers. The most common type of TC is papillary thyroid carcinoma (PTC), which is responsible for more than 80% of all cases of this type of cancer. Recently its incidence has considerably enhanced[1,2]. Besides ultrasonography and thyroid nodule aspiration biopsy under ultrasound guidance, which has led to more rapid detection of TCs in early stages, the importance of other factors in increasing the incidence of these malignancies needs to be investigated[3].

Currently, the risk factors for TC contain a history of radiation to the head and neck in childhood, genetic background[4], and inadequate or excessive iodine intake[5]. Although all of these risk factors are well-established, they do not justify the recent enhancement in the development of TC. In recent years, other parameters like insulin resistance, obesity, diabetes, and metabolic syndrome have been implicated in increasing the incidence of TC[6,7].

Other environmental factors, such as chemical toxins[8], and nutritional factors[9] have also been suggested as potential risk factors for TC.

Similar to thyroid cancer, the number of those who suffer from obesity has enhanced recently[10]. Numerous epidemiological research reported a significant correlation between obesity and TC[11,12]. A meta-analysis of four articles on TC showed that a 5 kg/m2 enhancement in the body mass index (BMI) increased the risk of TC [13]. Leptin is a common factor in obesity and thyroid cancer that is an adipokine secreted by the adipose tissue, regulating appetite and energy homeostasis [14, 15]. Obesity increases the body fat mass, which in turn increases the leptin concentration in blood circulation. The effects of leptin are exerted through binding to its receptors (OBRs) that can be found in different tissues [16].

In vitro studies have shown that leptin exerts anti-apoptotic and mitogenic effects on cancer cells of different cell lines. It can also act as an angiogenic factor [17]. Leptin and its receptors are overexpressed in many cancer cell lines[18]. Immunohistochemical studies have shown that leptin expression intensity is associated with the prognosis of different malignancies, like cancers of hepatocellular[19], colorectal [20], ovarian[21], prostate[22], breast[23], and glioblastoma [24].

A direct relationship between the hypothalamus-pituitary-thyroid axis and leptin has been shown in previous studies. Leptin stimulates the secretion of TSH and TSH has a stimulating effect on the secretion of leptin from adipose tissue. In addition, leptin is one of the effective factors in regulating TRH secretion from the hypothalamus [25-27]. Also, leptin has direct effects on thyroid hormones themselves. In the fasting state, T3 prevents the accumulation of leptin mRNA in fat cells, while the opposite of this situation is seen in the post-meal state[28]. On the other hand, previous research has proven that leptin itself increases the production of T3 by increasing the conversion of T4 to T3 [29].

Moreover, the results of previous studies showed that the serum leptin level was increased in cases with PTC than in healthy cases, regardless of BMI; on the other hand, the level of leptin decreased after total thyroidectomy [30, 31]. Another study reported the expression of OBR protein in 80% of patients with PTC. Increased OBR expression in PTC was associated with a more aggressive PTC phenotype in this study[32]. Overall, by increasing knowledge of the role of leptin in the pathogenesis of cancer, it is possible to produce anti-cancer drugs, which can modulate leptin signaling in the future [33-35].

Due to the limited studies available in this field and their contradictory results, this study aimed to evaluate the serum leptin level in patients with PTC before and after total thyroidectomy and to compare its concentration in these cases, patients with benign thyroid nodules and healthy cases.

MTERIALS AND METHODS

The current case-control research was carried out on euthyroid cases with malignant and benign nodules who were referred to endocrine clinics in Zahedan, Southeastern Iran, between August 2018 and October 2020.

The inclusion criteria were 1) Existence of thyroid nodules with a size greater than or equal to one centimeter 2) Normal thyroid function tests (normal free thyroxine [FT4: 0.8 -1.8 ng/dL]; normal free triiodothyronine [FT3: 2.3 - 4.2 pg/mL] and normal thyroid stimulating hormone [TSH: 0.4 - 4.2 mIU/L]) [36]. Exclusion criteria were: history of thyroid dysfunction, thyroid surgery, or previous reception of thyroid medications, history of radiation to the neck, and receiving contrast for imaging in the past 6 months. Moreover, if subjects had diabetes, liver failure, renal failure, or psychiatric disorders, they were excluded from the study. Women were excluded from the study if they received oral contraceptives, estrogen therapy, or if they were pregnant or breastfeeding.

All participants underwent ultrasound thyroid sonography by a sonologist using a 7.5-MHz linear probe. Fine needle aspiration biopsy (FNAB) was conducted for all nodules larger than or equal to one centimeter. An experienced cytologist evaluated all FNAB samples. The cytology was reported according to the Bethesda system[37]. According to the cytology result, the patients were in the group with PTC or the group with benign thyroid nodules. In all patients with PTC, after total thyroidectomy, positive permanent pathology confirmed the diagnosis. The participants in the control group were selected from

the hospital staff and non-first degree relatives of the patients in the case groups, after applying the inclusion and exclusion criteria. These subjects were apparently healthy and did not have evidence of any acute or chronic disease in their history and physical examination. Thyroid function tests and thyroid ultrasound were performed on all candidates in the control group. If they were euthyroid and no nodules of any size were reported in ultrasound entered the control group. The socio-economic level and geographical area of people in the control group were similar to the case group. Finally, three groups including the PTC group (91 patients), the benign nodules group (90 patients), and the control group (88 subjects) were included in the study.

From all participants, blood samples were obtained. For PTC patients blood sampling was repeated 12 weeks after total thyroidectomy when they were euthyroid with levothyroxine consumption. All blood samples were taken after 12 hours of fasting in the morning and were stored at -70 ° C until assay.

Thyroid function tests and serum levels of leptin were evaluated in patients with PTC before and after total thyroidectomy, as well as in patients with benign thyroid nodules and the control group. Lipid profile was measured in all participants. Serum leptin level was evaluated with Human Leptin ELISA Kit (ZellBio GmbH, Germany). Lipid kits (Pars Azmoon, Tehran, Iran) were used to measure lipids. FT4, FT3, and TSH using immunochemoluminescent assays by an automated analyzer (Diagnostic Products LIAISON, 2017, Italy) were measured.

All interventions were conducted following the ethical principles of the institutional as well as national research committee and with the 1964 Helsinki declaration and its later amendments. The Ethics Committee of Zahedan University confirmed the current study (IR.ZAUMS.REC.1399.079). All participants provided informed consent.

Statistical analysis

Quantitative variables are described as mean and standard deviation (SD), and qualitative variables are described as frequency and percentage. The Shapiro–Wilk test was used to check the normality of the variables. The One-way ANOVA test was used to assess the mean difference of numerical variables among the three studied groups (PTC, Benign nodule, and healthy control group). In addition, Post-hoc comparison was conducted based-on Bonferroni correction for pairwise comparison of these three groups. Chi-square or fisher's exact test was used to evaluate the relationship between two categorical variables. Moreover, the mean difference of a numerical variable in two groups of tumor size (T1 and >T1) was assessed with an independent t-test and Mann-Whitney U test for normality and non-normality distributed variables, respectively. The Pearson correlation was used for the assessment of the correlation between two numerical variables. P-value < 0.05 was considered statistically significant. Data were analyzed using Stata version 14.

RESULTS

A total of 91 patients with PTC were studied, 90 with BTN and 88 healthy euthyroid participants as control without nodules. In each group, more than 70% cases were female. The mean (SD) age was 24.38 (4.02) years in the PTC group; 24.20 (3.70) in the benign nodule group and 24.20 (3.91) for controls. The average BMI was 24 in three categories. Serum levels of FT4, FT3 were in their normal scale and we found no significant difference between the study groups. Although TSH was in the normal range in all three groups, it was significantly higher in PTC group. Serum levels of leptin in PTC group, benign group and in the control group were 22.34, 17.60 and 13.83 ng/ml, respectively, which was significantly higher in PTC patients than cases with benign nodules and controls (P<0.001) (Table 1). Figure 1 shows Serum leptin levels in patients with PTC, patients with benign thyroid nodules and control group.

Ninety-one patients with PTC were enrolled in the study. After TNM classification, 25.27 % patients had T1a, 29.67% T1b, 31.87% T2, 7.69% T3, 3.30% T4a and 2.20% T4b. Nodal metastases were observed in 15 patients while 76 patients had no metastases. No patients had distant metastases. 81.32% of patients were qualified as having stage I, 7.62% of patients had stage II, 4.40% had stage III, 5.49%, had stage IVa and 1.1% had stage IVb. Patients with PTC underwent total thyroidectomy and their leptin levels were remeasured 12 weeks after surgery

when they were euthyroid with levothyroxine consumption. The mean pre-thyroidectomy leptin level was 22.34 ± 6.21 ng/mL, and the mean post-thyroidectomy leptin level was 15.56 ± 4.25 with a Table 3 shows the comparison of clinical and biochemical parameters in patients with T1a and >T1a, although there was no significant difference in these parameters. We assessed the correlations between serum leptin and anthropometric and biochemical characteristics in PTC patients and considerable decline ($p < 0.05$). The declined level of leptin after thyroidectomy was higher than that of controls. Detailed profiles of the PTC patients is presented in Table 2.

patients with benign thyroid nodules. We observed significant associations with BMI, tumor size, and tumor stage in PTC patients. Also in patients with benign thyroid nodules, a correlation between BMI, tumor size, and leptin was observed (Table 4).

Table 1: Clinical and laboratory characteristics of study participants

Variable	PTC group Mean (SD);Median	Benign nodule Group Mean (SD);Median	Control group Mean (SD);Median	P		
				a	b	c
Number	91	90	88			
Sex (% women)	72 (79.12)	71 (78.88)	70 (79.54)	0.91	0.92	0.94
Age (years)	37.47(13.31);33	36.58(13.20);33	37.89(12.37);34	0.60	0.31	0.60
BMI (Kg/m^2)	24.38(4.02);23.9	24.20(3.70);23.9	24.20(3.91);23.85	0.81	0.87	0.96
FT4 (ng/dl)	1.29(0.28);1.3	1.30(0.21);1.35	1.26(0.19);1.3	0.43	0.14	0.41
FT3 (pg/ml)	3.50(0.50);3.6	3.64(0.69);3.5	3.71(0.67);3.7	0.06	0.24	0.15
TSH (mIu/L)	2.45(0.98); 2.3	1.88(1.04);1.55	1.62(0.88); 1.3	0.0000	0.29	0.0001
Total cholesterol (mg/dl)	176.61(36.42);165	153.42(41.68);152	155.21(40.58);152	0.0004	0.76	0.0002
LDL-C (mg/dl)	110.03(30.20);104	90.71(34.14);91.5	90.90(32.55);88.5	0.0000	O.98	0.0001
HDL-C (mg/dl)	47.63 (11.74);49	43.01(12.27); 39.5	43.86(11.83);44	0.05	0.55	0.03
Triglyceride (mg/dl)	98.38(52.63);83	102.13(67.71);79.5	100.03(61.41);80.5	0.54	0.78	0.58
VLDL (mg/dl)	19.75(10.72);17	20.65(13.89);16	19.98(12.10);17	0.65	0.82	0.74
Leptin (ng/ml)	22.34(6.21);21.9	17.60(3.24);17.51	13.83(2.95);13.55	0.0000	0.0000	0.0001

BMI: body mass index; FT4, free thyroxin; FT3, free triiodothyronine; TSH, thyroid stimulating hormone
LDL-C: low density lipoprotein-cholesterol; HDL-C: High density lipoprotein-cholesterol; VLDL: very low density lipoprotein
Data are shown as mean (SD) or percentage
[a]p value between PTC and control groups
[b]p value between Benign and control groups
[c]p value between three groups

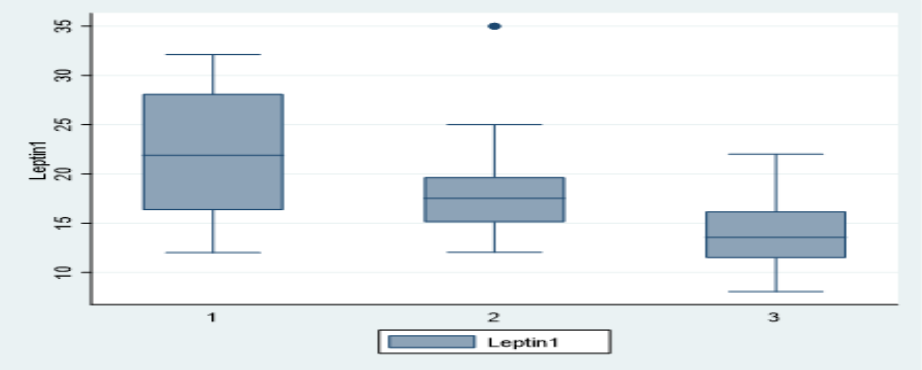

Figure 1. Serum leptin levels in patients with PTC (group 1), patients with benign thyroid nodules (group 2) and control group (group 3).

Table 2: Clinicopathological data of patients with papillary thyroid carcinoma

Clinicopathological characteristics	N (%)
No. of patients	91
Age (years)	37.47 (13.31)
≤ 34	49 (53.85)
> 34	42 (46.15)
Sex	
Female	72 (79.12)
male	19 (20.88)
Multifocality	
Absent	83 (91.21)
Present	8 (8.79)
Tumor size	
T1a	23 (25.27)
T1b	27 (29.67)
T2	29 (31.87)
T3	7 (7.69)
T4a	3 (3.30)
T4b	2 (2.20)
Nodal involvement	
N0	76 (83.52)
N1a	11 (12.09)
N1b	4 (4.40)
Distant metastasis	
M0	91(100)
M1	0
Stage	
I	74 (81.32)
II	7 (7.69)
III	4 (4.40)
IVa	5 (5.49)
IVb	1 (1.1)
IVc	0
Histological type	
Classic	76 (84.44)
follicular	13 (14.44)
Tall cell	1 (1.11)
Leptin (ng/ml) (before thyroidectomy) mean (sd)	22.34 (6.21)
Leptin (ng/ml) (after thyroidectomy) mean (sd)	15.56 (4.25)
TSH (mIU/l) (before thyroidectomy) mean (sd);median	2.45 (0.97);2.3
TSH (mIU/l) (after thyroidectomy) mean (sd);median	2.22 (1.04);2.1

Table 3: Comparison of anthropometric and biochemical parameters in patients with T1a and patients with > T1a

Variable	T1a Mean (SD); median	>T1a Mean (SD); median	P
Number	23	68	
Sex (% women)	19 (82.60)	53 (77.94)	0.63
Age (years)	38.78 (14.50); 35	37.02 (12.96); 33	0.66
BMI (Kg/m^2)	23.83 (2.77); 23.7	24.56 (4.37); 24	0.49
FT4 (ng/dl)	1.24 (0.19); 1.2	1.31 (0.31); 1.3	0.31
FT3 (pg/ml)	3.39 (0.45); 3.3	3.54 (0.51); 3.65	0.16
TSH (mIu/L)	2.12 (1.06); 1.8	2.56 (0.94); 2.45	0.05
Total cholesterol (mg/dl)	175.04 (42.50);174	177.14 (34.46);164	0.78
LDL-C (mg/dl)	108.08 (37.27);105	110.69 (27.71); 103	0.73
HDL-C (mg/dl)	45.60 (13.25); 45	48.32 (11.21); 49	0.35
Triglyceride (mg/dl)	109.43 (68.76); 87	94.64 (45.96); 83	0.59
VLDL (mg/dl)	22.08 (14.30); 17	18.97 (9.20); 16.5	0.62
Leptin (ng/ml) (before thyroidectomy)	20.53 (4.70); 19.32	22.95 (6.56); 23.75	0.12

BMI: body mass index; FT4, free thyroxin; FT3, free triiodothyronine; TSH, thyroid stimulating hormone
LDL-C: low density lipoprotein-cholesterol; HDL-C: High density lipoprotein-cholesterol; VLDL: very low density lipoprotein

Table 4: Correlations between serum leptin and anthropometric and biochemical characteristics in PTC patients and patients with benign thyroid nodules, separately**.**

Parameter	Patients with PTC		Patients with benign thyroid nodules	
	R	*P*	*R*	*P*
BMI	0.70	0.0000	0.32	0.0016
Total cholesterol	0.04	0.65	-0.0022	0.98
LDL-C	0.05	0.63	-0.02	0.85
HDL-C	-0.04	0.62	-0.05	0.61
Triglyceride	0.11	0.28	0.02	0.83
VLDL	0.13	0.20	0.0023	0.98
FT4	-0.05	0.62	0.03	0.71
FT3	0.01	0.90	0.01	0.89
TSH	0.18	0.07	0.15	0.14
Tumor size	0.21	0.04	0.30	0.0031
Tumor stage	-0.46	0.0000	-	-

Pearson correlation was used for correlation between prolactin and all normally distributed variables
A Spearman's correlation is used for correlation between leptin and non-parametric variables

DISCUSSION

This study showed that serum leptin levels were considerably higher in cases with PTC than those with BTNs, as well as euthyroid controls without nodules. This study also suggested that serum leptin level was considerably higher in cases with BTNs compared with controls. In PTC patients, serum leptin levels decreased after thyroidectomy.

These results are consistent with other previous studies [30, 38]. In this regard, Akinci et al.[30] showed leptin levels were increased in PTC patients and declined following total thyroidectomy. We found that leptin in PTC patients was associated with higher BMI, larger tumor size, and a higher tumor stage. Similar observations have been reported in other studies [39, 40]. In a study by Cheng et al. [39], leptin and its receptors were associated with increased tumor size and lymph node metastasis. In addition, according to Uddin et al. [40], the presence of OBR was correlated with an aggressive phenotype. On the other hand, a study by Warakomski et al. reported no significant relationship between the serum leptin level and tumor size [41].

As mentioned earlier, recently, the incidence of TC has enhanced around the world. Besides the known risk factors, other potential risk factors for TC have been suggested [8, 9, 42, 43]. Similar to TC, the incidence of obesity has enhanced during the past years[44]. Leptin has been suggested as one of the factors, linking obesity to a higher incidence of cancer. It is known that an increase in body fat mass elevates the secretion of leptin from adipose tissue and increases its serum concentration. Its primary role is to reduce appetite and stimulate energy expenditure by exerting an effect on the central nervous system[45]. Leptin has anti-apoptotic and mitogenic effects on various cancer cells [46].

The importance of hyperleptinemia in colon, hepatocellular, and breast cancers is well established in the literature[17]. Leptin often acts through Ob-R receptor (encoded by db gene).

Obesity as an inflammatory process is associated with increased secretion of various cytokines from adipose tissue. Among these cytokines, leptin has been the most studied. Leptin acts as an anti-apoptotic factor in many cell types. Its role in many cancers related to obesity is due to its pro-angiogenic and pro-inflammatory effects and its mitogenic function [33]. The impact of leptin on the pathogenesis of a wide range of cancers is exercised through the JAK/STAT pathway. Various functions have been attributed to this pathway including modulation of PI3K/AKT3 and ERK1/2 signaling[47], increase in systemic inflammation through increased TNF-α and IL6, increase in expression of antiapoptotic proteins[48], increase in angiogenic parameters like vascular endothelial growth factor (VEGF) and increase in expression hypoxia inducible factor-1a (HIF-1a), Which is involved in cancer cell proliferation, migration, and survival [49].

In available limited studies, increased OBR expression has been demonstrated in PTC patients. This increase was associated with a more aggressive phenotype of PTC, such as metastasis to lymph node, a larger tumor size, extrathyroidal extension, a higher metastatic stage, tall-cell histology, greater persistence, and recurrence of cancer, and lower disease-free survival rates [32]. The addition of leptin to cancer cells in PTC can promote cell growth, inhibit apoptosis, and modulate cancer cell migration. In patients with PTC, it has been shown that increasing OBR expression increases the expression of X-linked inhibitor of apoptosis protein (XIAP, an anti-apoptotic protein) [50].

Thyroid dysfunction can indirectly cause changes in the serum leptin level by changing the body composition, intermediary metabolism, and basal energy expenditure[51]. Accordingly, serum leptin levels were measured in patients with PTC at 12 weeks after total thyroidectomy when they were being treated with levothyroxine and were euthyroid based on thyroid function tests. The results showed that serum leptin levels significantly decreased after surgery, compared to the preoperative stage.

Previous studies have shown that increased BMI and insulin resistance are risk factors for benign nodule formation[52]. However, there is limited information regarding the association between leptin and benign thyroid nodules. In this study, we found a considerable difference in serum leptin levels between the BTN and control groups. This finding is contrary to the results of a study by Seven et al., which showed that the serum level of leptin was more stable in cases with BTNs than in controls [53].

The present study has limitations. The number of participants was relatively limited. On the other hand, the strengths of the current research included having age, gender, and BMI matched controls without thyroid nodules. Cytological evaluation and pathological outcome assessment were other strengths of this study.

CONCLUSION

In conclusion, serum leptin levels were considerably higher in cases with PTC than in those with BTNs as well as a control group. This study showed the significant correlation of leptin with BMI, tumor size, and tumor stage in PTC patients. The serum leptin level decreased in PTC patients after thyroidectomy. Leptin can be considered a potential tumor marker for papillary thyroid cancer.

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CONFLICT OF INTEREST

The authors declare no conflicts of potential interest in conducting this research and its publication.

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