RESEARCH ARTICLE

Interleukin-13 and Immunohistochemical Study of Iraqi Patients with Thyroid Goiter

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Received: 02nd January, 2022; Revised: 25th January, 2022; Accepted: 27th February, 2022; Available Online: 25th March, 2022

ABSTRACT

Thyroid goiter is a type of autoimmune disease and complex endocrine system, which includes a number of diseases that share a cellular and humoral immune response leading to functional impairment and thus an increase in gland size. As it represents 90% of thyroid diseases. A current study was designed to investigate the effect of interleukin-13 (IL-13) on thyroid goiter in Iraqi patients, as well as its relationship with the receptor of the programmed cell death process (TNF-related apoptosis-inducing ligand (TRAIL)) and the role of them in the occurrence of the disease. Forty samples of peripheral blood were collected from Iraqi women with Thyroid goiter diagnosed by endocrinologists at Baghdad Teaching Hospital, Medical City for the period from 1/1/2019 to 1/4/2019 with mean age of 42.6 ± 7.8 years, to estimate IL-13 concentration using enzyme-linked immunoassay (ELISA) technique, while 30 blood samples were taken from healthy females as a control group with matched ages to patients. Also, forty biopsies were collected from the thyroid gland of the same patients after completion of the total thyroidectomy to study the expression of thyroid tissues for TRAIL marker using Immunohistochemistry (IHC). Statistical analysis of results showed a significant increase in IL-13 level in the patients (183.21 ± 23.04 pg/mL) compared to controls (169.62 ± 32.52 pg/mL). With respect to immunohistochemical study, it was obvious that there is a significant difference in TRAIL expression among patients group and it has been observed a direct correlation between IL-13 level and TRAIL expression, an increase of IL-13 concentration (191.80 ± 25.59) was simultaneously with the increased expression of TRAIL 3 (50%) ($p < 0.034$), which confirm the potential role of IL-13 in stimulating TRAIL expression in thyroid tissue and thus the incidence of Thyroid goiter. Also, results showed a significant correlation between IL-13 level and the patient's family history of autoimmune thyroid diseases (AITDs), while there was no significant correlation between IL-13 level and the patient's family history of type1 Diabetes mellitus and smoking. On the other hand, a significant correlation between IL-13 concentration and TSH in patients sample were detected ($p < 0.001$), with no correlation with FT4 concentration in both patients and controls ($p < 0.05$). Receiver operating characteristic (ROC) curve analysis showed that the level of IL-13 in the patient samples and controls is a weak diagnostic tool for diagnosing Thyroid goiter except the concentration of 147.4723 pg/mL with a sensitivity of 100%, 30% specificity and 167.8581 pg/mL (sensitivity 70%, specificity 70%). In conclusion, IL-13 level and its correlation with TRAIL expression in Iraqi patients with Thyroid goiter may play a vital role in the pathogenesis of disease.

Keywords: IL-13, Thyroid goiter, Thyroid hormones, TNF-related apoptosis-inducing ligand (TRAIL).

International Journal of Drug Delivery Technology (2022); DOI: 10.25258/ijddt.12.1.49

How to cite this article: Jafar AM, Hussein IA, Al-Assaf AIS, Sulaiman TI. Interleukin-13 and Immunohistochemical Study of Iraqi Patients with Thyroid Goiter. International Journal of Drug Delivery Technology. 2022;12(1):260-265.

Source of support: Nil.

Conflict of interest: None

INTRODUCTION

Thyroid goiter is one of the endocrine system and autoimmune diseases.[1] It may be present in different thyroid pathologies, such as non-toxic nodular goiter (NTNG) or Hashimoto's thyroiditis (HT), as a result of focal hyperplasia of thyrocytes (nodal goiter) or generalized enlargement of thyroid (diffuse goiter).[2] Autoimmune thyroid diseases AITDs are the most common organ-specific autoimmune diseases, affecting 2-5% of the world's population.[3] Cytokines are defined as peptides, soluble glycoproteins or proteins that are small in size and of low molecular weight (5-30 kDa), and are produced by many (mostly) immune cells and non-immune cells and include: interleukins, chemokines, interferons and tumor necrosis factors that have a wide range of multiple effects on different organs.[4] Cytokines also play a critical role in autoimmune thyroid diseases AITDs by regulating immune responses that affect the balance between autoimmune tolerance and triggering autoimmune diseases.[5] As a result of the role they

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play in the immune system and direct targeting of the thyroid gland cells, Cytokines play a major role in the pathogenesis of AITDs.[6] Interleukin 13 (IL-13) is a pluripotent cytokine produced by Th2 cells, as well as by many cells including Th1 and Th17 cells, mast cells, basophils, eosinophils, and natural killer T cells (NK).[7,8] Its plays a major role in asthma, allergy, and autoimmune diseases.[9,10] Although genetic and environmental factors play an important role in autoimmune diseases, the increase in the percentage of thyroid cells suffering from apoptosis in Hashimoto's thyroiditis (HT), compared to the decrease in their percentage in Graves' disease (GD), suggests that apoptosis had a role in the functional regulation and cellular growth of thyroid cells.[11] In addition, cytokines play a role in inducing apoptosis leading to AITDs.[12] Studies have also shown that the death receptor pathway including tumor necrosis factor receptor TRAIL plays a major role in the development of thyroid autoimmune diseases.[13-15] This study is the first investigation in Iraq that deals with the relationship of IL-13 and TRAIL among Iraqi patients with Thyroid goiter with the aim to determine their role in this disease pathogenesis.

MATERIALS AND METHODS

A total of 40 benign Multi-nodular goiter women (10 having a family history of Grave's disease, 7 having a family history of Hashimoto's thyroiditis and 23 with no history of AITDs) and their main age ± S.E. was 42.6 ± 7.8 years, attending Baghdad Teaching Hospital, Medical city, Iraq during the period January-April 2019 were enrolled in this study, in addition to 30 healthy women (controls), their main age ± S.E. was 41.3 ± 6.9 years. They were clinically examined and evaluated by the consultant medical staff. 3.5 mL of peripheral blood were collected (in a clotting tubes for the purpose of serum isolation) from patients and controls to estimate the concentration of IL-13 by ELISA using the Quantikine ELISA kit (R&D Systems, Minneapolis, MN, USA). 40 thyroid tissue biopsies were taken from the same patients after completion of the total thyroidectomy and kept in (10% formalin solution) for 24 hours in order to prepare them for cutting, histological examination and immunohistochemical staining to study the expression of thyroid tissues for apoptosis marker TRAIL. Tissue sections were prepared, and the slides were stained[16] with some modification, then slides were examined under a compound light microscope with different magnification powers and the selected sections were photographed using the digital camera connected to the microscope and the calculator. In respect to immunohistochemical, TRAIL expression was detected using Human Anti-TRAIL antibody kit (Pathnsitu Biotechnologies Pvt Ltd, India) through labeled streptavidin-biotin method.[17] The percentage of TRAIL-positive cells was used to assess the test result. 10 microscopically fields were examined under 400X magnification, for each field the number of positive and negative cells was counted. Then the average was extracted for each, the result was expressed as the percentage of positive cells from the total number of cells for each patient.[18] Results were statistically analyzed using the Statistical Package for the Social Sciences (SPSS) program, version 26 of 2013. One Way-ANOVA test or the Students-t-test was used to compare the differences in the mean of aggregates (quantitative data) at ($p < 0.05$).[19] The significant difference between percentages (qualitative data) was also measured using the Pearson Chi-square test (χ^2-test) with Yate's correction.[20]

RESULTS AND DISCUSSION

By using ELISA, results showed a significant increase in IL-13 level in patients sera (183.21 ± 23.04 pg/mL) compared to controls (169.62 ± 32.52 pg/mL, also there was significant differences between the percentages of IL-13 level in the patients and controls at ($p < 0.05$) using the Chi-square test (Table 1 and Figure 1), this may be due to increased expression of Th2 as a result of the influence of environmental factors on these cells in patients with genetic susceptibility to goiter.[21]

The study showed a significant association between IL-13 concentration level and TSH, where the high level of IL-13 concentration was directly proportional to the high concentration of TSH in patients compared to controls,

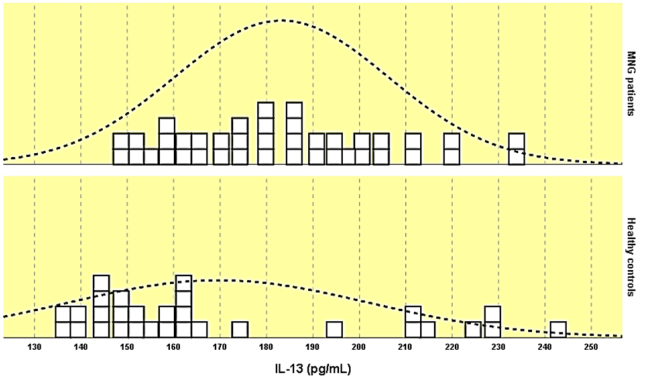

Figure 1: IL-13 concentration level (pg./mL) in sera of Thyroid goiter patients and the control groups.

Table 1: IL-13 concentration level (pg/mL) in sera of Thyroid goiter patients and the control groups.

	Patients		*Control*		
IL-13 level (pg/mL)	*No.*	*%*	*No*	*%*	*p value*
<150	2	5	11	36.7	0.005*
150	6	15	5	16.7	
160	5	12.5	5	16.7	
170	6	15	1	3.3	
180	7	17.5	-	-	
190	4	10	1	3.3	
200	4	10	-	-	
210	3	7.5	3	10	
=>220	3	7.5	4	13.3	
Mean ± SD	183.21 ± 23.04		169.62 ± 32.5		0.0001*
Range (Higher value-Lower value)	235.03–147.55		242.87–135.28		

* = Significant difference between the percentages at the probability level ($P < 0.05$) using the Chi-square test.
# = Significant difference between two averages at the probability level ($P < 0.05$) using Students-t test.

while there was no significant association between IL-13 concentration level and FT4 concentration in patients and controls at probability level ($p < 0.05$) as in Table 2. The expulsion proportionality of IL-13 and TSH concentration, according to our opinion, is due to the role of IL-13 in stimulating programmed cellular death process in thyroid tissue, resulting in TSH not entering the thyroid gland and accumulating in blood, which eventually leads to the occurrence of Subclinical Hypothyroidism (SCH), which is characterized by a higher level of TSH concentration in the blood than normal, while FT4 concentration remains within normal.[22]

By using ANOVA-test, results revealed a significant correlation between IL-13 level in patients and the family history of AITDs at ($p < 0.004$), as there was a significant increase in the level of IL-13 in patients with a family history of Graves' disease, also there was a significant decrease in IL-13 level in patients with a family history of Hashimoto's disease when compared them to its level in patients with no family history of AITDs (Table-3), these results are in agreement with other researches[23] that showed an increase in IL-13 secretion in one third of patients with Graves' disease. While other study[24] showed an elevated incidence of IL-13 in tears of TAO patients. In addition, we did not notice through results a significant correlation between IL-13 level with type 1 diabetes patients and smoking at ($P < 0.05$) (Table-3), which showed that IL-13 was not affected by smoking and has no effect on β-cells in the pancreas of patients. These results differ with other research results,[25] which indicated the role of IL-13 in reducing the occurrence of apoptosis in beta cells as well as protecting primary beta cells from apoptosis. While a study[26] suggested that IL-13 protected beta-cell by activating the STAT6 pathway that induces transcription of several anti-apoptotic genes in beta-cells. On the other hand, a study[27] indicated that exposure of children suffering from asthma to cigarette smoke by smoking parents increases the secretion of IL-13 in children. Also, it has been indicated[28] that the increase in IL-13 concentration may contribute to increased intra-bronchial mucus secretion in smokers with chronic bronchitis (CB).

Receiver operating characteristic (ROC) curve analysis was performed to determine whether there was an additional advantage of using the study parameters for predicting Thyroid goiter, that could be used as an indicator of the disease to prepare for the subsequent accurate diagnosis and the ability to determine the "final value" of the sensitivity and optimal specificity of the variable, which is an indicator of the incidence of the disease from while knowing the value of an area under curve (AUC), the value 0.9 means (excellent indicator), 0.8 means (good indicator), 0.7 means (average index), 0.6 means (weak indicator) and the value is <0.6 means (not suitable as an indicator). The test results showed that the level of IL-13

Table 2: The relationship between IL-13 concentration (pg/mL) and Thyroid-stimulating hormone concentration and Free Thyroxin in patients and controls.

IL-13 concentration pg.\ml				
Control		*Patients*		*TSH*
Mean ± SD	*No.*	*Mean ± SD*	*No.*	*ml unit\L*
162.54 ± 22.35	7	166.32 ± 6.79	2	1
164.19 ± 36.69	12	171.72 ± 12.87	11	2
180.04 ± 33.11	11	170.96 ± 15.82	11	3
-	-	204.38 ± 28.67	5	8
-	-	205.75 ± 15.46	6	9
-	-	194.00 ± 24.84	5	10
0.422+		0.001 ^		Value P
Mean ± SD	*No.*	*Mean ± SD*	*No.*	*FT4 Ng.\Dc*
164.13 ± 31.94	16	179.22 ± 24.53	20	0.5
172.25 ± 36.38	9	188.87 ± 19.24	16	1
182.41 ± 29.21	5	180.55 ± 30.85	4	1.5
0.542+		0.457+		Value P

Table 3: Relationship between IL-13 level (pg/mL) and family history of AITD, type 1 diabetes and smoking for goiter patients and the control group.

		IL-13 level (pg/mL)			
		Patients		*Control*	
Family history for patients and control		*No.*	*Mean ± SD*	*No.*	*Mean ± SD*
Type 1 Diabetes	Patients	11	185.68 ± 25.23	-	
	Non patients	29	182.28 ± 22.43	30	169.62 ± 32.52
	p value	0.682+		+	
Family history of autoimmune Thyroid diseases (AITDs)	Graves' disease	10	199.71 ± 21.30		-
	Hashimoto's thyroiditis	7	164.27 ± 11.95		-
	Non patients	23	181.81 ± 21.83		-
	p value	0.004 ^		-	
Smoking	Smokers	8	185.20 ± 16.82	-	
	Non smokers	32	182.728 ± 24.55	30	169.62 ± 32.52
	P value	0.789+		+	

^ = Significant difference between more than two independent means at the probability level ($P < 0.05$) using ANOVA.
+= There were no significant differences using ANOVA analysis.

concentration in the patient sample and the controls is a weak diagnostic tool for diagnosing Thyroid goiter except the concentration of 147.4723 (pg/mL) with a sensitivity of 100%, 30% specificity and 167.8581 pg/mL (sensitivity 70%, specificity 70%). The optimal indicator of sensitivity and specificity was considered the "ultimate value" and the concentration is 180.6112 pg/mL (sensitivity 50%, specificity 73.3%) (Table 4 and Figure 2).

Histological sections showed the presence of inactive follicular thyroid cells with colloid accumulation within the lumen of the thyroid follicles which are of different sizes, lined with cubic epithelial cells, and some of the follicles are irregularly dilated (Figures 3, A & B).

Immunohistochemical staining results showed TRAIL expression by thyroid tissue (Figures 4, 5 and 6) and percentages of expression grade 1, 2, and 3 were 12.5% and 37.5% and 50%, respectively (Table 5). This expression demonstrates the role of the TRAIL pathway in the destruction of thyroid tissue through inducing apoptosis in patients with thyroid goiter. These results are in agreement with those of[29] which demonstrated the role of TRAIL in inducing apoptosis in follicular cells of thyroid tissue and thus destruction of thyroid tissue in subjects with goiters. Other research[30] indicated that

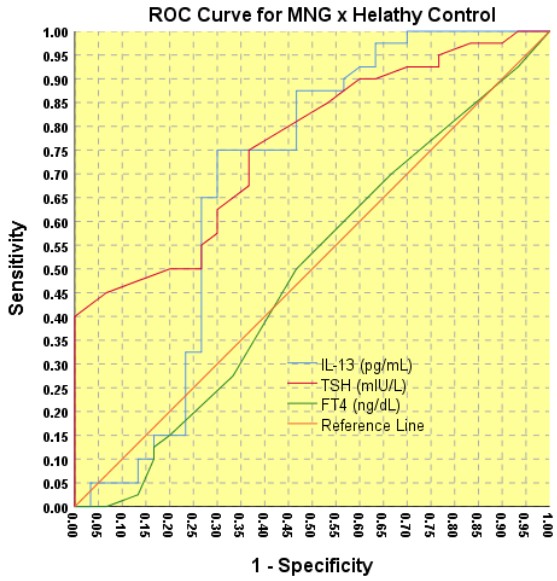

Figure 2: ROC curve, demonstrates sensitivity and specificity to IL-13 concentration level, Thyroid stimulating hormone (TSH) and Free Thyroxin (FT4) in Thyroid goiter patients and controls.

Table 4: Area under curve and confidence limits for IL-13 concentration level, Thyroid Stimulating hormone and Free Thyroxin for Thyroid goiter patients and controls.

95%Confidence limits 95% فقيشلا دودح					
Maximum	*Minimum*	*p-Value*	*Standard error*	*Area under curve*	*Test result variables*
0.830	0.549	0.007	0.071	0.690	IL-13
0.870	0.650	0.000	0.056	0.760	TSH
0.652	0.372	0.868	0.071	0.512	FT4

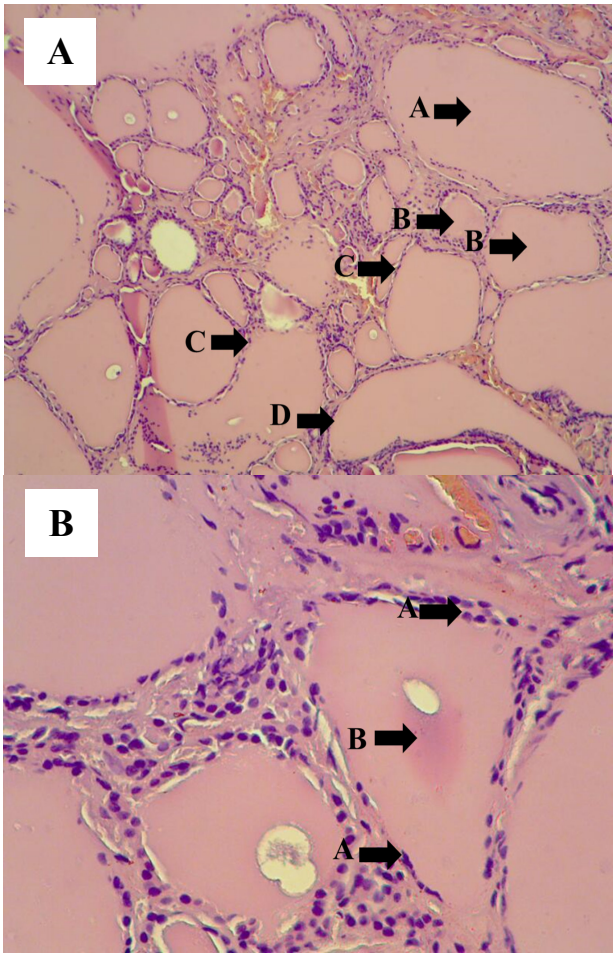

Figure 3: Cross-section of Thyroid tissue in patients with Thyroid goiter showing the presence of A) inactive follicular thyroid cells with colloidal accumulation within the lumen of the thyroid follicles, B) Which are of different sizes, C) Lined with cuboidal epithelial cells, D) and some vesicles are irregularly dilated. Hematoxylin and eosin stain A (100 X), B (400 X).

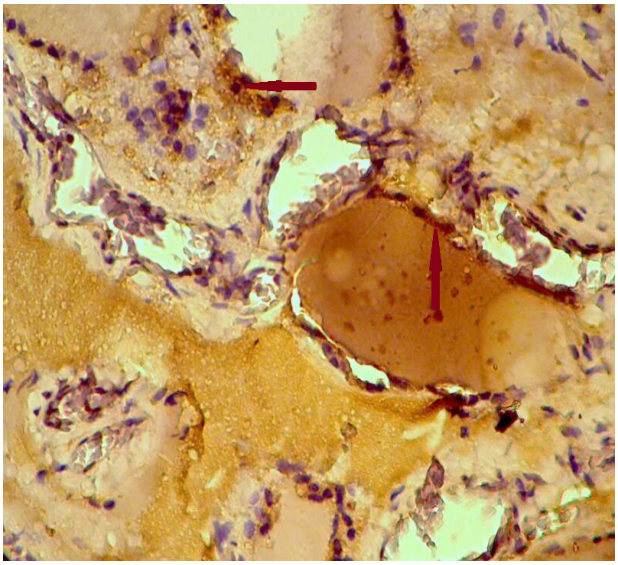

Figure 4: Cross-section of Thyroid tissue in patients with Thyroid goiter showing the presence of brown pigments in the apical membrane and cytoplasm of thyroid follicular cells (IHC score +1) (400 X).

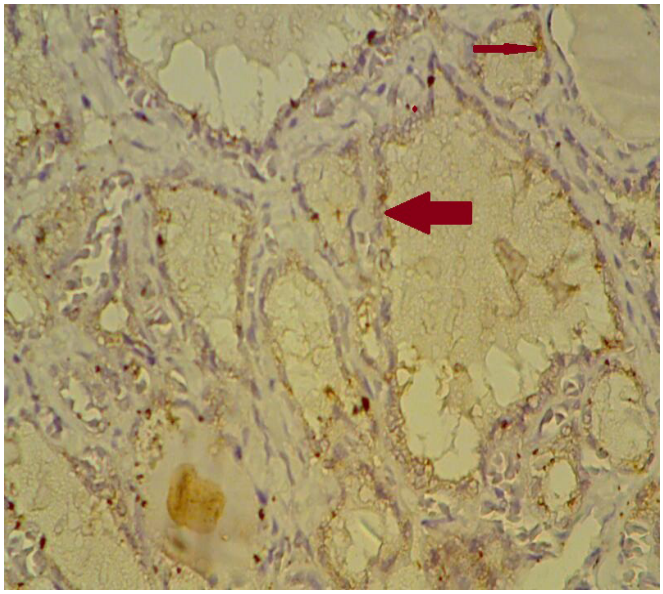

Figure 5: Cross-section of Thyroid tissue in patients with Thyroid goiter showing the presence of brown pigments in the apical membrane of thyroid follicular cells (IHC score +2) (400 X).

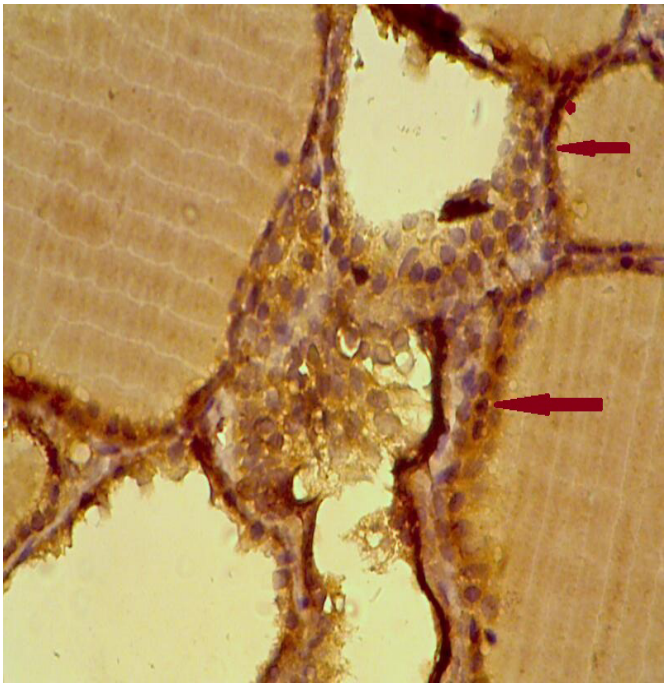

Figure 6: Cross-section of Thyroid tissue in patients with Thyroid goiter showing the presence of brown pigments in the apical membrane of thyroid follicular cells (IHC score +3) (400 X).

(TNFα), it could cause apoptosis in cultured epithelial thyroid cells, as well as, there was a significant direct correlation between the intensity of stimulation and the degree of TRAIL receptors expression on the surfaces of epithelial thyroid cells.

By using ANOVA-test, results showed a significant decrease in IL-13 level in patients whose thyroid tissue expressed TRAIL 1 and 2 (20.19 ± 183.3, 171.73 ± 15.06 pg/mL respectively) compared to its level in patients whose thyroid tissue expressed TRAIL 3 (± 25.59 191.8006 pg/mL) at ($p < 0.034$) (Table 6), which shows the possible role of IL-13 in inducing the expression of TRAIL in thyroid tissue and thus the occurrence of goiter.[31] Showed a significant correlation between the concentration of Th2-secreted cytokines including IL-13 and the expression level of TRAIL in saliva of patients with asthma. Other study[32] revealed that IL-13 induced apoptosis in lung epithelial cell lines and primary lung epithelial cells, which leads to damage the epithelial tissue of bronchi and loss of its function and thus the occurrence of asthma.

Table 5: Percentages of thyroid tissue expression of TRAIL in patients with Thyroid goiter.

TRAIL expression		
IHC score	*No.*	*%*
1	5	12.5
2	15	37.5
3	20	50

Table 6: IL-13 concentration (pg/mL) in Thyroid goiter patients' serums with TRAIL expression degree in thyroid tissue.

IL-13 level (pg/ml)		
Degree of TRAIL expression in Thyroid tissue	*No.*	*Mean ± SD*
1	5	183.31 ± 20.19
2	15	171.73 ± 15.06
3	20	191.80 ± 25.59
P value	0.034 ^	

^ = Significant difference between more than two independent means at the probability level ($p < 0.05$) using ANOVA.

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