Plant Archives Volume 20 No. 2, 2020 pp. 6101-6108 **e-ISSN:2581-6063 (online), ISSN:0972-5210**

ROLE OF CYTOKINES IN THE PATHOGENESIS OF THYROID DISEASE AMONG IRAQI PATIENTS

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Abstract

Autoimmune thyroid diseases, comprising the two main entities Hashimoto's thyroiditis and Graves' disease, are the most common autoimmune diseases. The objective of this research was to study the relationship between some selected cytokines and thyroid dysfunction. The present study included 80 patients with thyroid disease (55 hypothyroidism and 25 hyperthyroidism) and 20 apparently healthy control subjects in a case-control study, at age ranged between (20-80) years old. Blood samples of those subjects were collected during the period from September 2019 to April 2020. Case information sheets involving Age, Sex, Family History, Pregnancy, Diabetic, smoking, Urinary Tract Infection, Gastric Infection. Results of demographic data found that the presence of minor differences in mean age of control subjects, hypothyroid patients and hyperthyroid patients, 41.6, 42.78 and 40.36 years, respectively, the difference was statistically insignificant ($P = 0.655$). The effect of thyroid dysfunction on body mass index, urinary tract infection (UTI), diabetes mellitus (DM) and positive rheumatoid factor in patients was studied. The mean body mass index (BMI) was higher in hypothyroid patients than in hyperthyroid patients, 29.35 kg/m^2 versus 22.51 kg/m^2, respectively in a highly significant manner ($P < 0.001$). Urinary tract infection (UTI) was statistically insignificant ($P = 0.427$). Diabetes mellitus (DM) was the difference in rate of DM was statistically insignificant ($P = 0.782$). The positivity for rheumatoid factor (RF) was limited to hypothyroid patients as it was seen in 3 (5.5%) and no one of patients with hyperthyroidism exhibited positivity to RF (0.0 %); however, because of low number of positive RF patients in hypothyroid group, the difference was statistically insignificant in comparison with hyperthyroid patients ($P = 0.584$). The frequency distribution of control subjects and patients with hypothyroidism and hyperthyroidism exhibited no significant variation ($P = 0.099$).

Key words: Thyroditis, hypothyrodism, hyperthyrodism, body mass, RF.

Introduction

Thyroiditis is defined as an inflammatory disorder of the thyroid gland. It may result from a myriad of etiologies and Is usually classified into acute, sub-acute, and chronic form. Each of these is associated with a distinct clinical presentation and histology. Medical therapy remains the mainstay of the management of thyroiditis, but surgical treatment is warranted in certain specific circumstances (Orlo*, et al.,* 2016).

The term thyroiditis implies an inflammatory response, and although inflammation of the thyroid may be present in some forms of thyroiditis, in reality some etiology of thyroiditis are not actually an inflammatory response. Form of thyroiditis may share some features but may have distinct underlying etiology, including autoimmune, infectious, drug or radiation related, induced by trauma, or related to invasive fibrotic thyroiditis (Riedel¼s thyroiditis) (Gregory W.R., *et al*., 2020).

Thyroid disorders are among the most common endocrine diseases and are often primary due to damage of the thyroid gland itself (Zaccarelli-Marino MA, *et al*., 2016). Their global prevalence is estimated at 10% and are by far dominated by subclinical or asymptomatic forms (hypo- or hyper-thyroidism); overt or symptomatic forms are much rarer (Bouomrani S., *et al*., 2019).

Autoimmune thyroid disease (AITD) is a prototypical organ specific autoimmune disease. The etiology of AITD is multifactorial; interactions between genetic and environmental predisposing triggers lead to dysregulation

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of immune tolerance. The incidence of the two main clinical presentations of AITD, Graves disease (GD) and Hashimoto's thyroiditis (HT), is estimated at 5% of the population. (Antonelli, *et al*., 2015; Yoo S.W. and Chung K.H., 2019).

Autoimmune thyroid diseases, comprising the two main entities Hashimoto's thyroiditis and Graves' disease, are the most common autoimmune diseases and are often observed together with other autoimmune diseases. (Rojas, *et al*., 2012) This has led to the hypothesis that many patients with autoimmune disease, in general, suffer from an underlying dysfunction of critical mechanisms ensuring self tolerance (Bliddal, *et al*., 2017).

Hashimoto's thyroiditis and Graves' disease are two very common organ-specific autoimmune diseases which are characterized by the presence of circulating thyroid antibodies and infiltration by autoreactive lymphocytes of the thyroid gland, and occasionally the orbit. In this setting, an immunological overlap with other autoimmune diseases and a family history, mainly in females, are frequently found. It has been traditionally thought that HT is mainly mediated by a cellular autoimmune response, with a strong inflammatory infiltrate, which leads to destruction and resultant failure to function of the thyroid gland. On the other hand, GD has mainly been considered to be mediated by a humoral autoimmune response, mainly due to the presence of autoantibodies directed against the thyrotropin receptor (TRAb) which stimulate the growth and function of thyroid follicular cells (TFCs), thus leading to development of goiter and hyperthyroidism. However, as in other autoimmune disorders, humoral and cellular immune mechanisms are closely related and cross-linked in AITD.(Rapoport B. and McLachlan S.M., 2014; González-Amaro R*., et al.,* 2015).

Material and Methods

Patients: Eighty thyroiditis patients were clinically-diagnosed, newly diagnosis treated (25) hyperthyroidism and (55) hypothyroidism, at age ranged between (20-80) years old, taking from out-patient in clinic private of Babylon Province during the period from December 2019 to (April) 2020 were included as the test group. In addition, (20) non-thyroiditis (apparently healthy) age matched patients attending the outpatient clinic were recruited as control subjects. Case information sheets involving Age, Sex, Family History, Pregnancy, Diabetic, smoking, Urinary Tract Infection, Gastric Infection.

Blood Sample Collection: A volume of 5 ml of blood was collected from vein of patient then sterile cotton was placed over the injection site as the needle was removed. The blood was immediately placed 2.5ml in gel tube without anticoagulant and placed 2.5ml in EDTA tube , and then transported to the laboratory for additional analysis (Lewis S. and Bain B., 2001).

Separation and Preservation of Serum: The blood sample was allowed standing for 2 hours at room temperature for clotting then centrifuged at 3000 rpm for 5 minutes. The serum was collected carefully by sterile pipette and decanted into sterile Eppendrof test tube. The collected serum was stored at -20°C until using for serological tests (Lewis S. and Bain B., 2001).

Rheumatoid factors (RF) Assay: This test was done by RF- latex slide agglutination. The RF reagent is a suspension of polystyrene latex particles sensitized with specially prepared human IgG. The reagent is based on an immunological reaction between human IgG bound to biologically inertlatex particles and RF in the test specimen. When serum containing RF was mixed with the latex reagent, visible agglutination occurs. The RFlatex reagent sensitivity was adjusted to detect a minimum of 8 IU/mL of RF according with the WHO International Standard without previous sample dilution.

Interleukin 6 Assay in Serum:T his test done by IL6 ELISA kit [BioAssay Technology Laboratory (BTL) Human Interleukin 6 ELISA Kit].The standard curve range (2ng /L-600ng /L), Sensitivity (1.03ng / L), size 96 wells used for the ELISA. This IL-6 enzyme linked immunosorbent assay (ELISA) applies atechnique called a quantitative sandwich immunoassay.

Results and Discussion

Demographic characteristics of control subjects and patients with thyroid disease

The present study included 20 apparently healthy control subjects and 80 patients with thyroid disease, 55 of whom were diagnosed to have hypothyroidism and 25 of whom where categorized as having hyperthyroidism. The demographic characteristics of enrolled subjects have been outlined in table 1.

The mean age of control subjects was 41.6 years and their age has ranged from a minimum of 31 to a maximum of 61 years. The mean age of hypothyroid patients was 42.78 years and it ranged from a minimum of 20 to a maximum of 75 years. In addition, the mean age of patients with hyperthyroidism was 40.36 years and the age was ranging from 24 to 63 years. Despite the presence of minor differences in mean age of control subjects, hypothyroid patients and hyperthyroid patients, 41.6, 42.78 and 40.36 years, respectively, the difference was statistically insignificant (P = 0.655), as shown in

Table 1: Demographic characteristics of control subjects and patients with thyroid disease.

Characteristic	Control $n = 20$	Hypothyroidism $n = 55$	Hyperthyroidism $n = 25$	P
Age (years)				
Mean ±SD	41.60 ±9.06	42.87 ±12.96	40.36 ±9.46	0.654 †NS
Range	31-61	20-75	24-63	
BMI (kg/m^2)				
Mean ±SD		29.35 ±5.44	22.51 ±3.60	<0.001 €HS
Range		20-48.3	17.1-29.6	
Gender				
Male, *n* (%)	0 (0.0 %)	11 (20.0 %)	4 (16.0 %)	0.099 ¥NS
Female, *n* (%)	20 (100.0 %)	44 (80.0 %)	21 (84.0 %)	

n: number of cases; SD: standard deviation; †: One way ANOVA; €: independent samples t-test; ¥: Chi-square test; NS: not significant at $P > 0.05$; HS: highly significant at $P \leq 0.01$

table 1.

Regarding body mass index, in hypothyroid patients it ranged from 20-43.3 kg/m^2, whereas, in hyperthyroid patients it ranged from 17.1-29.6 kg/m^2. On the other hand, the man body mass index (BMI) was higher in hypothyroid patients than in hyperthyroid patients, 29.35 kg/m^2 versus 22.51 kg/m^2, respectively in a highly significant manner ($P < 0.001$), as shown in table 1. Healthy control subjects were all women, hypothyroid group included 11 (20.0 %) men and 44 (80.0 %) women, and hyperthyroid group included 4 (16.0 %) men and 21 (84.0 %) women. The frequency distribution of control subjects and patients with hypothyroidism and hyperthyroidism exhibited no significant variation ($P = 0.099$), as shown in table 1.

In this study, the mean age of control group, hypothyroid group and hyperthyroid group were 41.6, 42.78 and 40.36 years, respectively and there was no significant difference in mean age among enrolled groups. The lack of significant difference in mean age between control group and study group is mandatory in such case control study to avoid bias in results attributed to variation in age; therefore, the current study enrolled age matched study and control subjects.

Regarding body mass index, in the present study, the mean BMI of hypothyroid patients was the highest followed by control group and then finally by hyperthyroid group. The mean BMI of hypothyroid patients and hyperthyroid patients was 29.35 kg/m^2 versus 22.51 kg/m^2, respectively. It is obvious that, in this study, hypothyroid patients were mostly overweight or obese, whereas, hyperthyroid patients were either lean or underweight. Indeed this finding is consistent with the finding of previous authors (Ríos-Prego *et al*., 2019; Sanyal and Raychaudhuri, 2016). Valyasevi *et al*., in 2002 explained the association between TSH and BMI by that TSH may directly stimulate preadipocyte differentiation resulting in adipogenesis. Rotondi *et al*., in 2009 added that the impact of body weight on thyroid differs according to lower grades of overweight and morbid obesity.

The association between TSH and BMI was explained by (Chan, *et al*., 2003.) to be under the influence of adipose tissue signals and leptin may have significant effects on central regulation of thyroid function through TRH. (Zimmermann-Belsing, *et al*., 2003) suggested that a positive correlation between serum leptin and TSH also indicates a positive correlation between BMI and TSH. Several studies revealed that fat cells and precursor forms have receptors for TSH. The signal is transferred with the activation of cAMP-dependent kinase resulting in adipocyte precursor differentiation in adipocytes and lipogenesis (Schäffler *et al*., 2005; Valyasevi *et al*., 2002).

Conversely, hyperthyroidism has traditionally been associated with weight loss and underweight (Amouzegar *et al*., 2018). Subjects with hyperthyroidism have an adrenergic hyperstimulation with increased basal metabolism and thermogenesis and a greater overall energy expenditure resulting in a tendency toward weight loss. Hyperthyroidism can also induce an increased gastrointestinal transit and occasionally anorexia due to the anorexigenic effect of triiodothyronine (Karmisholt *et al*., 2011). All these factors may have lead to the belief of a direct association of hyperthyroid states with low weight (Ross *et al*., 2016).

In the current study, control subjects were all women and most of patients with thyroid disease, whether hypothyroidism or hyperthyroidism, were women. There was also no significant difference in the distribution of patients and control subjects with respect to gender ensuring statistical matching regarding gender to avoid any bias in the results resulting from variation in gender distribution. As it is obvious, in the current study, most patients were women in accordance with the vast majority of published articles dealing with thyroid disease (Diab *et al*., 2019; Olmos *et al*., 2015; González-Rodríguez *et al*., 2013; Ladenson *et al*., 2000).

Primary hypothyroidism is up to 8–9 times more common in women than in men, and the prevalence increases with age, with a peak incidence between the ages of 30 and 50 years (Aoki *et al*., 2007). In the US, hypothyroidism affects an estimated 4% of women aged

18–24 years and 21% of women older than 74 years; respective values in men are 3% and 16% (Canaris *et al*., 2000). A UK survey determined that approximately 7.5% of women and 2.8% of men have elevated serum levels of TSH, while a Danish population study found that the lifetime risk of overt hypothyroidism was 4.1% in women and 1.3% in men (Chiovato *et al*., 2019).

All forms of thyroid diseases are much more frequently observed in women than men, although the reasons are still not completely elucidated (Gessl *et al*., 2012). The female-to-male rate ratio is reported at 4~6:1 for autoimmune thyroiditis and about 3~4:1 for thyroid nodule. The effects of female gonadal hormones and X chromosome inactivation on thyroid gland and immune system greatly contribute to the female predilection of autoimmune thyroiditis. The former mainly include prolactin and estrogen. The direct actions of estrogen on the thyroid tissue contribute to the development of thyroid goiter, nodule and cancer in women (Li and Li, 2015).

Rates of urinary tract infection (UTI), diabetes mellitus (DM) and positive rheumatoid factor in patients with thyroid disease

Rates of urinary tract infection (UTI), diabetes mellitus (DM) and positive rheumatoid factor in patients with thyroid disease were demonstrated in table 2. Urinary tract infection (UTI) was seen in 6 (10.9 %) hypothyroid patients and 5 (20.0 %) hyperthyroid patients, and the difference in rate of UTI was statistically insignificant ($P = 0.427$).

Diabetes mellitus (DM) was encountered in 2 (3.6 %) hypothyroid patients and 2 (8.0 %) hyperthyroid patients, and the difference in rate of DM was statistically insignificant ($P = 0.782$). The positivity for rheumatoid factor (RF) was limited to hypothyroid patients as it was seen in 3 (5.5 %) and no one of patients with hyperthyroidism exhibited positivity to RF (0.0 %); however, because of low number of positive RF patients in hypothyroid group, the difference was statistically insignificant in comparison with hyperthyroid patients ($P = 0.584$), as shown in table 2.

Urinary tract infection was seen in both hypothyroid and hyperthyroid patients enrolled in this study. In accordance with present study, a previous case report by (Correia, *et al.,* 2019) has raised the issue between hypothyroidism and recurrent urinary tract infection. Most hypothyroid patients are middle-aged women. They may develop retention of urine and renal failure. This retention could be the presenting symptom or may be found incidentally in a patient who has other signs and symptoms of hypothyroidism like myxedema, malaise, a change in the tone of voice, and mental confusion (Alizadeh *et al*., 2013).

Thyrotoxicosis is characterized by exaggerated responses to catecholamines, while in hypothyroidism, narrowing of adaptive responses is observed. It is, therefore, not surprising to lower urinary tract symptoms in patients with thyroid dysfunction (Alizadeh *et al*., 2013). Hyperthyroidism is also more common among women. Patients may exhibit both irritative and obstructive urinary symptoms. Of the urinary symptoms, urinary frequency is the most common. Other storage symptoms include urgency, urge incontinence, nocturia, and enuresis (either primary or secondary). Of the voiding symptoms, incomplete emptying and straining have been reported. Patients rarely complain of urgency, frequency, and enuresis; therefore, they should be asked about these symptoms in moderate to severe cases of hyperthyroidism (Alizadeh *et al*., 2013).

Diabetes mellitus was also seen in both hypothyroid and hyperthyroid patients enrolled in this study. Diabetes mellitus (DM) and thyroid dysfunction (TD) often tend to coexist in patients. Both hypothyroidism and hyperthyroidism are more common in type 2 diabetes mellitus (T2DM) patients than in their nondiabetic counterparts (Kalra *et al*., 2019). Autoimmunity can explain the common linkage between T1DM and autoimmune thyroid diseases; however, the linkage between T2DM and TD is more complicated (Kalra *et al*., 2019).

Circulating thyroid hormones affect several different organs and cells, have a major impact on glucose, lipid, and protein metabolism, and can worsen glycaemic control in T2DM. Hyperthyroidism and thyrotoxicosis can worsen subclinical DM and cause hyperglycaemia in T2DM patients, increasing the risk of diabetic complications. T2DM reduces thyroid-stimulating hormone levels and impairs the conversion of thyroxine (T4) to triiodothyronine (T3) in the peripheral tissues (Kalra *et al*., 2019).

Table 2: Rate of urinary tract infection (UTI), diabetes mellitus (DM) and positive rheumatoid factor in patients with thyroid disease.

Characteristic	Hypothyroidism *n* = 55	Hyperthyroidism *n* = 25	*P*
Urinary tract infection (UTI)	6 (10.9 %)	5 (20.0 %)	0.427 YNS
Diabetes Mellitus (DM)	2 (3.6 %)	2 (8.0 %)	0.782 YNS
Positive rheumatoid factor (RF)	3 (5.5 %)	0 (0.0 %)	0.584 FNS

Data were expressed as number and %; *n*: number of cases; Y: Yates correction; F: Fischer exact test; NS: not significant at $P > 0.05$

The pathophysiological association between T2DM and TD is believed to be the result of interplay between various biochemical, genetic, and hormonal malfunctions. Increased expression of the hepatic glucose transporter type 2 gene (GLUT2) is found in hyperthyroidism. Intracellular triiodothyronine (T3) may also play a role in insulin sensitivity. It mediates the action of the GLUT4 gene in skeletal muscles and increases basal and insulin-mediated glucose transport. Homozygosity for the Thr92Ala polymorphism of the deiodinase type 2 (DIO2) gene also enhances the risk for T2DM (RayandGhosh, 2016; Wang, 2013).

Both hypothyroidism and hyperthyroidism were associated with diabetes mellitus and urinary tract infection; however, positivity to rheumatoid factor in the current study was limited to hypothyroid patients. Previous studies observed that thyroid dysfunction was prevalent in RA patients, with the prevalence ranging from 6 to 34% (Cárdenas Roldán, *et al*., 2012; Przygodzka and Filipowicz-Sosnowska, 2009). In one case-control study, 65 RA patients and 550 matched healthy individuals were investigated to evaluate the relationship between RA and thyroid dysfunction and the results indicated that patients with RA were likely to have increased prevalence of both hyperthyroidism and hypothyroidism, especially overt hypothyroidism (Li, *et al*., 2019). The exact mechanism underlying the relationship between RA and thyroid disorders is still unclear. As autoimmune diseases, the etiology of RA and AITD are complex, both genetic and environmental factors are involved. In line with this, autoimmune diseases generally share similar pathological pathways, which implies the possible aggregation phenomenon of autoimmune diseases. Some gene variations were found to exert great effect in the pathogenesis of both RA and AITD (Li, *et al*., 2019).

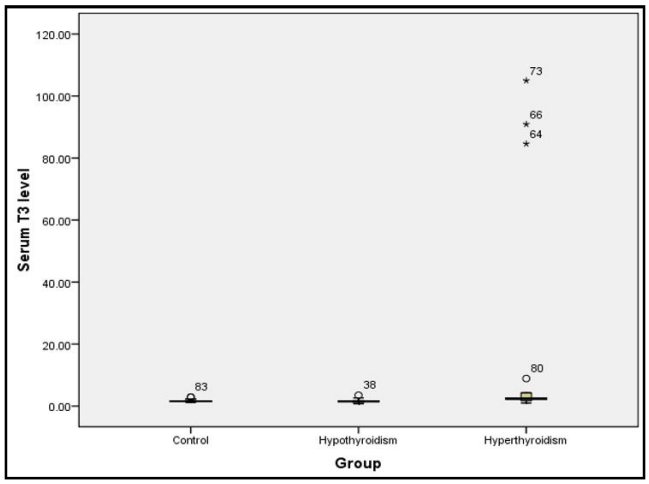

Fig. 1: Box plot showing comparison of serum T_3 among control subjects, patients with hypothyroidism and patients with hyperthyroidism.

Serum hormonal levels of T3, T4 and TSH in control subjects and patients with thyroid disease

Serum hormonal levels of T3, T4 and TSH in control subjects and patients with thyroid disease were outlined in table 3. Control subjects showed narrow range of variation in serum T3 as it ranged from 1.26 -2.9 and the mean and median were 1.74 and 1.58, respectively. Patients with hypothyroidism showed serum T3 level in the range of 0.73 - 3.5 with a mean of 1.16 and a median of 1.53. On the other hand, some patients in hyperthyroid group had extremely high serum T3 level; therefore the range was surprisingly wide form 1 to 105. The mean serum T3 in Hyperthyroid group was affected by those extreme values and became high (13.59); however, the median T3 of hyperthyroid group was 2.40, which is higher than both control and hypothyroid group significantly ($P< 0.001$), as shown in Fig. 1.

Regarding serum T4, it ranged from 64.7 - 109.51, 24.96 -141.1 and 1.33 -320, in control group, hypothyroid group and hyperthyroid group, respectively. The mean level of serum T4 was 93.63, 82.36 and 135.57, in control group, hypothyroid group and hyperthyroid group, respectively. There was highly significant variation in serum T4 among study groups, being highest in hyperthyroid group and lowest in

Table 3: Serum hormonal levels of T3, T4 and TSH in control subjects and patients with thyroid disease.

Hormone Serum T3	**Control** ***n*** **= 20**	**Hypothyroidism** ***n*** **= 55**	**Hyperthyroidism** ***n*** **= 25**	***P***
Mean ±SD	1.74 ±0.50	1.61 ±0.54	13.59 ±30.31	<0.001
Range	1.26 -2.9	0.73 -3.5	1 -105	KHS
Median (IQR)	1.58 (0.46)B	1.53 (0.62)C	2.40 (2.57)A	
Serum T4				
Mean ±SD	93.63 ±13.81	82.36 ±22.66	135.57 ±78.97	<0.001
Range	64.7 -109.51	24.96 -141.1	1.33 -320	KHS
Median (IQR)	99.20 (15.25)B	83.30 (24.60)C	118.00 (54.10)A	
Serum TSH				
Mean ±SD	1.74 ±0.96	11.34 ±15.17	0.72 ±1.21	<0.001
Range	0.94 -4.21	0.3 -60	0.01 -3.8	KHS
Median (IQR)	1.33 (1.12)B	6.14 (7.82)A	0.10 (0.76)C	

n: number of cases; SD: standard deviation; IQR: inter-quartile range; TSH: thyroid stimulating hormone; K: Kruskal Wallis test; HS: highly significant at *P* d" 0.01; Capital letters were used to indicate the level of significance after Mann Whitney U test between any two groups so that similar letters indicate no significant difference whereas different letters indicate significant difference and letter (A) takes the highest value

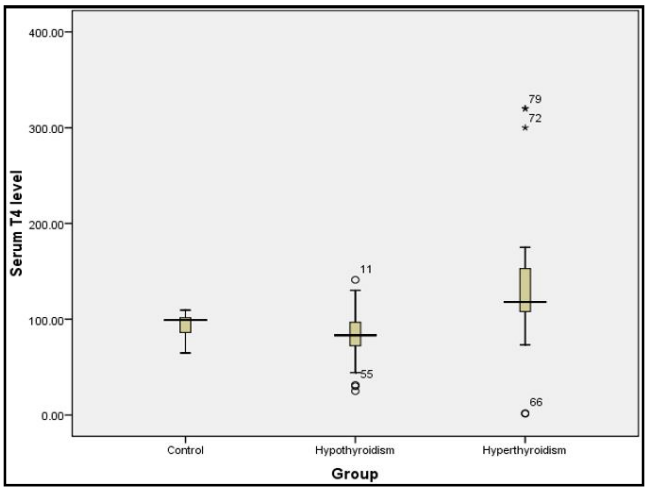

Fig. 2: Box plot showing comparison of serum T_4 among control subjects, patients with hypothyroidism and patients with hyperthyroidism.

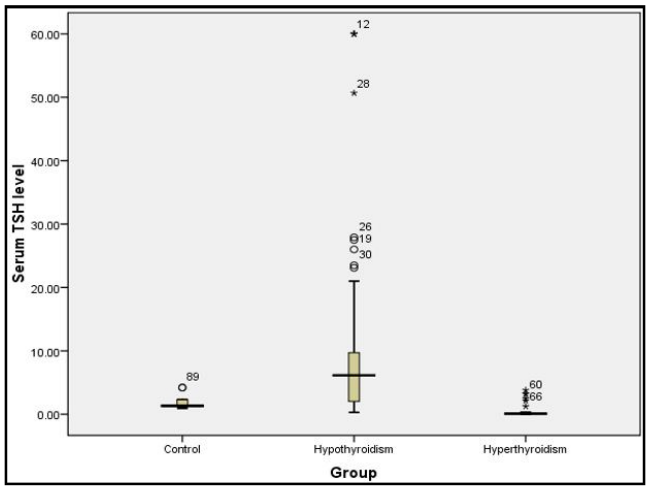

Fig. 3: Box plot showing comparison of serum TSH among control subjects, patients with hypothyroidism and patients with hyperthyroidism.

hypothyroid group, as shown in Fig. 2.

Regarding serum TSH, it ranged from 0.94 - 4.21, 0.3 - 60 and 0.01 - 3.8 in control group, hypothyroid group and hyperthyroid group, respectively. The mean TSH level was 1.74, 11.34 and 0.72 in control group, hypothyroid group and hyperthyroid group, respectively. There was highly significant variation in serum TSH among study groups, being lowest in hyperthyroid group and highest in hypothyroid group, as shown in table 3 and Fig. 3.

In the current study, the levels of serum T3 and T4 were normal in control group, low in hypothyroid group and high in hyperthyroid group; whereas, serum TSH levels were normal in control group, high in hypothyroid group and low in hyperthyroid group. These findings indicate that the majority of cases with hypothyroidism enrolled in the current study were primary hypothyroidism indicating an abnormality in thyroid gland leading a low production of T3 and T4 and subsequently stimulating the pituitary gland to secrete more TSH. On the other hand, these findings indicate that the majority of cases with hyperthyroidism enrolled in the current study were primary hyperthyroidism indicating an abnormality in thyroid gland leading a high production of T3 and T4 and subsequently suppressing the pituitary gland TSH secretion.

Table 4: Interleukin -6 (IL-6 among control subjects, patients with hypothyroidism and patients with hyperthyroidism.

Characteristic	Hypothyroidism *n* = 55	Hyperthyroidism *n* = 25	*P*
IL-6			
Mean ±SD	87.05 ±101.82	102.40 ±171.26	0.093 MNS
Range	34.76 -637.77	27.17 -681.37	
Median (IQR)	61.60 (18.80)	55.79 (22.05)	

n: number of cases; SD: standard deviation; IQR: inter-quartile range; M: Mann Whitney U test; NS: not significant at $P > 0.05$

Serum IL-6 has ranged from 34.76 -637.77 in hypothyroid group and from 27.17 -681.37 in hyperthyroid group. The mean serum IL-6 was 87.05 in hypothyroid group and 102.40 in hyperthyroid group. The median serum IL-6 was 61.60 in hypothyroid group and 55.79 in hyperthyroid group. There was no significant difference in mean serum IL-6 among study groups ($P = 0.093$), as shown in table 4 and Fig. 4.

In the current study, the serum IL-6 level was higher in hypothyroid group in terms of median value, than in hyperthyroid group; however, the difference was statistically insignificant. Increased serum interleukin-6

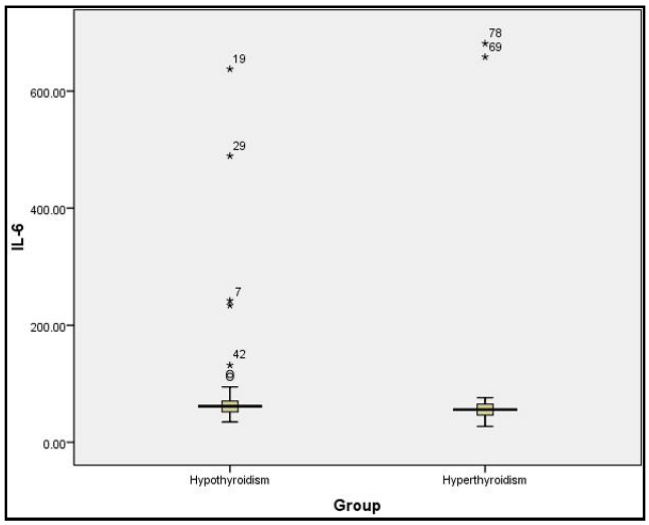

Fig. 4: Box plot showing comparison of serum IL-6 between patients with hypothyroidism and patients with hyperthyroidism.

(IL-6) concentrations have been reported in patients with thyroid destructive processes. A previous study has shown increased level of serum IL-6 as well as IL-6 soluble receptor in patients with Graves's disease, an autoimmune thyroiditis with hyperthyroid manifestation (Salvi, *et al*., 1996). The author in the later study attributed the source of IL-6 to be the thyroid gland and stated that the production of IL-6 by thyroid follicular cells is stimulated by TSH and TSH antibodiestherefore, measurement of serum IL-6 in patients with autoimmune thyroiditis, particularly Grave's disease, may be of diagnostic and prognostic value. It has been shown in an experimental study that serum IL-6 in combination with soluble IL-6 receptors can inhibit thyroid function, but, IL-6 alone has no such effect (Yamazaki, *et al*., 1996).

Increased serum interleukin-6 (IL-6) concentrations have been reported in patients with subacute thyroiditis and in some patients with amiodarone-induced thyrotoxicosis, possibly because of cytokine release from damaged thyroid cells (Bartalena, *et al*., 1994). In one study, it was found that the increase in serum IL-6 level in patients with Graves disease and patients with non-functioning thyroid nodule, following radioactive iodine and fine needle aspiration, respectively, was comparable indicating that the destruction of thyroid gland is the reason for rise in serum IL-6 (Bartalena, *et al*., 1994) and this can explain the current study finding of lack of significant difference in the level of serum IL-6 between hypothyroid and hyperthyroid patients because the source of IL-6 is the follicular cells that have underwent destruction by autoimmune thyroiditis in both Hashimotos thyroiditis and Grave's disease.

On the other hand, experimental work has shown that Thyroid-Stimulating Hormone Induces Interleukin-6 Release from Human Adipocytes through Activation of the Nuclear Factor-κB Pathway and this may explain the rise in serum IL-6 in patients with hypothyroidism (Tayze *et al*., 2008).

Ethical approval and consent

All subjects involved in this work are informed and the agreement will obtained verbally from each one before the collection of samples. This study was approved by the committee on publication ethics at college of medicine, University of Babylon, Iraq, under the reference No. **BMS/0231/016**

Acknowledgment

The authors acknowledge the members and staff all private laboratories participate in study research In Babylon province for helping in collecting the samples, data and their excellent technical assistance. Authors also thank all patients who participated in this study.

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