ORIGINAL ARTICLE

Correlation of Cytokines with Thyroid Hormones and Autoantibodies in Thyroid Autoimmune Diseases

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ABSTRACT

Background: *The autoimmune thyroid diseases (AITDs), like hyperthyroidism Graves' Disease (GD) and hypothyroidism Hashimoto's Thyroiditis (HT), are common occurrence autoimmune disease associated with thyroid hormones and immunity (autoantibodies and cytokine like IL-27 and IL-1β) disturbance.* ***Objective:*** *The aim of current study is to study and determine the relation of IL-27 and IL-1β cytokines with thyroid hormones and autoantibodies.* ***Methodology:*** *150 participants in total (50 GD, 50 HT, and 50 control) all between the ages of 20 and 60 were attending Al-Sader Teaching Hospital in Al-Najaf. The ELISA kits were used to measure levels of IL27 and IL1β (MyBioSource, USA), and levels of thyroid hormones fT3, fT4, TSH (Elabscience firm, USA), whereas autoantibodies (TR Ab, TPO Ab, and Tg Ab) were measured by Cobas e411 instrument.* ***Results:*** *the patients were insignificantly more female; significantly older; and significantly had family history, body mass index, abnormal weight, urban residence than control. However, significantly (P=0.001) the levels of fT3 fT4 were high in GD and low in HT, and vice versa in TSH. The immunity including autoantibodies (TR Ab, TPO Ab, and Tg Ab) and Cytokine (IL27 and IL1β) were significantly (P=0.001) dysregulated and have increased level in GA and HT than control. The are positive correlation of IL27 and negative correlation of IL-1β with most parameters.* ***Conclusion:*** *AITDs resulted from immunity dysfunction and underlined by correlation of cytokine IL-27 and IL-1β with thyroid hormone and autoantibodies, however, TSH had positive correlation with IL-27 in HT and negative correlation with IL-1β in GD.*

INTRODUCTION

Autoimmune thyroid disorders (AITDs), such as Graves' disease (GD) and Hashimoto's thyroiditis (HT), are grave ailments marked by abnormal autoimmunity responses targeted against thyroid gland. The complex interplay between immune system anomalies, environmental variables, and genetic vulnerabilities results in thyroid tissue injury and failure [1]. AITDs are associated with disturbance of thyroid hormone, which are thyroid stimulating hormone (TSH), free triiodothyronine hormone (fT3), and free thyroxine hormone (fT4), moreover AITD are frequently related with the existence of autoantibodies (Abs) to several thyroid antigens, such as thyrotropin receptor (TR), thyroid peroxidase (TPO), and thyroglobulin (Tg) [2]. Hyperthyroidism in GD is caused by thyroid-stimulating autoantibodies to the TSH (thyrotropin) receptor (TR Ab), whereas hypothyroidism in HT is associated with thyroid peroxidase and thyroglobulin autoantibodies but no TR Ab [3].

The TR Ab may mimic or block the activity of TSH or be functionally neutral, so stimulating TR Abs are specific biomarkers for Graves disease (GD) and responsible for many of its clinical manifestations [2]. In another hand, Thyroid peroxidase (TPO) enzyme is required for the synthesis of thyroid hormones, and any alterations might result in a deranged thyroid profile. However, in some cases such as GD and HT, auto-antibodies may also be formed against TPO [4,5]. In respect of Thyroglobulin (Tg) is a large glycoprotein gathered in the follicular colloid of the thyroid gland, where it acts as a substrate for the manufacture thyroid hormones, the polyclonal antibody (Tg Ab) mostly IgG developed due to present of Thyroglobulin antigen [6].

The studies revealed that ATID pathogenesis is resulted from cytokines level disturbance, as important examples are IL27 and IL-1β. The IL27 as a member of the IL6/IL12 family of cytokines, affects immune cells

innate and adaptive immunity through various pleiotropic actions[7]. The producers of IL27 are dendritic cells, monocytes/macrophages and other antigen-presenting cells [8]. The correlation between IL27 and several autoimmune disorders, including rheumatoid arthritis, multiple sclerosis, and inflammatory bowel disease, has brought attention to the significance of IL27 in immune-mediated diseases [9]. However, little is understood regarding its specific function in AITDs, particularly GD and HT.

Interleukin-1 (IL-1) family with two primary agonist peptide members of IL-1α and IL-1β is affiliated to IL-1R with dual characteristics of pro-inflammatory [10]. Likewise, immune cells and inflammation are affected preponderantly in regard with the pro-inflammatory cytokine IL1-Beta [11]. It is mainly produced by activated macrophages and plays a critical function as an endogenous mediator of both the acute-phase and chronic inflammatory response [12]. It has been revealed that excessive signaling of the IL1-Beta gene has been linked to various AITDs. This pathway leads to the enhanced production of autoantibodies and inflammation of the thyroidal tissue [13]. More studies are required for understanding specific signal mechanisms through which IL1-Beta contributes to the pathological process of GD and HT though its existence is confirmed. In this case-control study, the IL27 and IL1-Beta levels in GD and HT patients were assessed and compared to thyroid hormones fT3, fT4 and TSH, and autoantibodies TRAb, TPO Ab and Tg Ab to explore any association and to further investigate the roles of these cytokines in AITD and whether they can be used as diagnostic, prognostic or therapeutic targets markers.

METHODOLOGY

Study population:

A total of 150 participants (50 GD, 50 HT, 50 controls) aged between 20 and 60 years was recruited in a sequential manner from Al-Sader Teaching Hospital in Al-Najaf during March to August, 2023. In terms of ethnicity and other factor, the sampling was done in such a way that it represented the given population. A comprehensive survey including different areas of concern and response to lifestyle factors and the demographics data were administered to sample groups to look at the people. All participants signed a written informed consent and the study conducted in accordance with Declaration of Helsinki and the rules set down by the research committee of the medical ethics sections in Ministry of Health Iraq.

Blood sample collection and analysis:

Under aseptic condition the blood specimens were collected then centrifuged for five minutes at 3000 rpm to extract serum, which was frozen at -20°C in two Eppendorf tube repeaters. Thyroid function blood tests (fT3, fT4, TSH) were conducted using the complete automated Chemiluminescence Immunoassay feature of the Cobas e411 instrument. The enzyme-linked immunosorbent test (ELISA), developed by the Elabscience firm (USA), was used to evaluate the serum concentrations of thyroid autoantibodies (TR ab, TPO Ab, Tg Ab) and ELISA kit from MyBioSource (USA) was used measure the serum cytokine levels of IL27 and IL1β in subjects.

Statistical Analysis:

Entering, organizing, and analyzing participant data including those with autoimmune thyroid disease and controls was done using IBM's 2017 SPSS version 25 software for Windows. Before being analyzed, each variable was examined for errors or inconsistencies. The significance of differences in the frequency of qualitative variables between thyroid patients and controls was assessed using the Chi-square test. While the t test was used compare the mean values of age and BMI and F test (ANOVA) was used to compare mean of fT3, fT4, TSH, TR Ab, TPO Ab, Tg Ab, IL27, and IL1β parameters between the patients with GD and HT against control group. Moreover, R^2 was used to study relation between IL27 and IL1β thyroid hormones and autoantibodies. The threshold for significance (P-value) was set at 0.05 or less. In addition, the Microsoft Word 2013 for Windows program was used to exhibit the outcomes and discoveries in tables.

RESULTS

Socio-demographic characteristics:

Table (1) displays the distribution of subjects into two categories: patients (GD and HT) and control. In respect of age, the patients were significantly older and the patients' second 40–60-year group (GD 22, HT 17) was significantly (P <0.05) more susceptible than first 41–60-year age group (GD 28, HT 33).

However thyroid patients' group have more family history (GD 12, HT 9; P <0.001), female (GD 28, HT 26; P >0.05), body mass index (P <0.05), abnormal weight (GD 31, HT 28; P <0.05) and urban residence (GD 33, HT 23; P <0.05) than control.

Table 1: Socio-demographic characteristics of study population

Characteristic	Patient *n* = 100	Control *n* = 50	P-Value
Age (years)			
Mean ±SD	42.4±9.4	37.7 ± 10.12	***t*, P<0.05**
20-40 *n* (%)	39 (39)	22 (44)	¥, P<**0.05**
41-60 *n* (%)	61 (61)	28 (56)	
Family history			
Positive, *n* (%)	21 (21)	0 (0.0)	¥, P<**0.001**
Negative, *n* (%)	79 (79)	50 (100)	
Sex			
Male, *n* (%)	46 (46)	30 (60)	
Female, *n* (%)	54 (54)	20 (40)	¥, P>**0.05**
Body mass index (BMI)			
Mean ±SD	29.4±5.5	25.13 ± 3.08	***t*, P<0.05**
Normal Weight	41 (41)	20 (40)	†, P<**0.05**
Abnormal Weight	59 (59)	30 (60)	
Residence			
Urban, *n* (%)	56 (56)	19 (38)	
Rural, *n* (%)	44 (44)	31 (62)	¥, P<**0.05**

n: number of cases, **SD**: standard deviation, ***t***: t test, †: ANOVA test, **¥**: Chi-square test.

Measurement of thyroid hormones:

The current study's Figure (1) showed that fT3 and fT4 were very high significantly (P=0.001) higher (lower) in GD (HT) than control, meanwhile TSH showed a very significant (P=0.001) increased (decreased) level in HT (GD) than control.

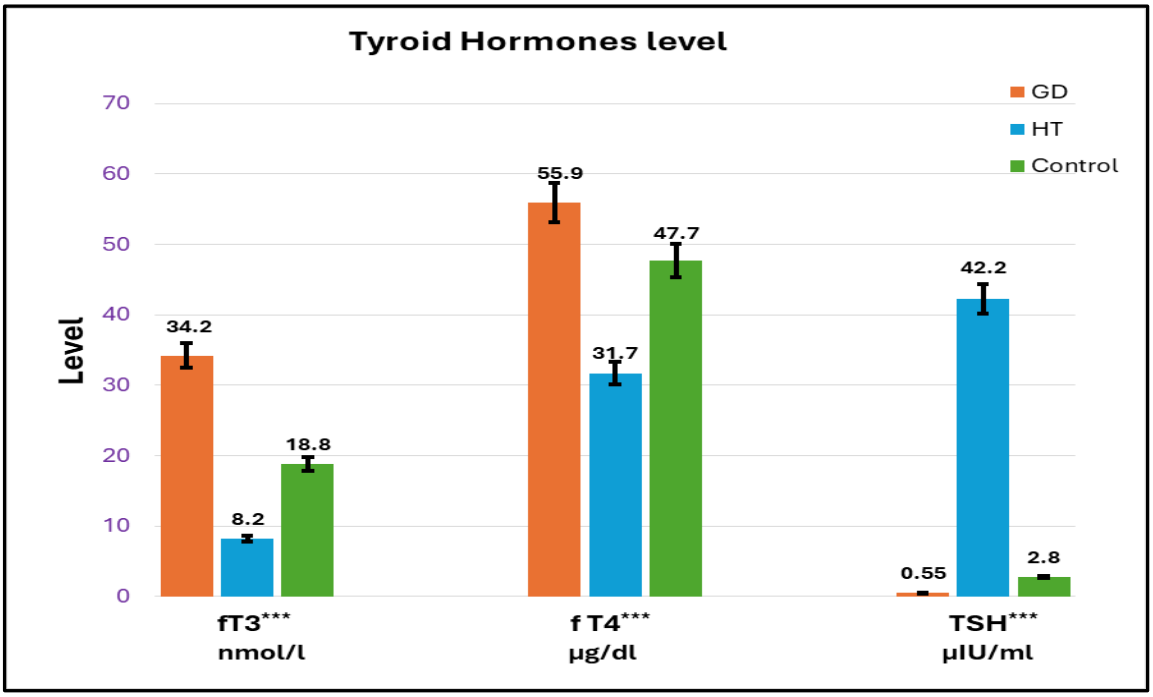

Fig 1: The mean concentration of thyroid hormones among studied groups. GD: Graves' disease**, HT:** Hashimoto thyroiditis**, fT3**: free triiodothyronine hormone, **fT4**: free thyroxine hormone**, TSH:** Thyroid stimulating hormone, ***:** Very high significant.

Measurement of autoantibodies level:

Figure (2) shows a significantly (P=0.001) raised level of TR Ab and Tg Ab in GD than HT and control, but TPO Ab mean was significantly (P=0.001) more in HT followed by GD then control.

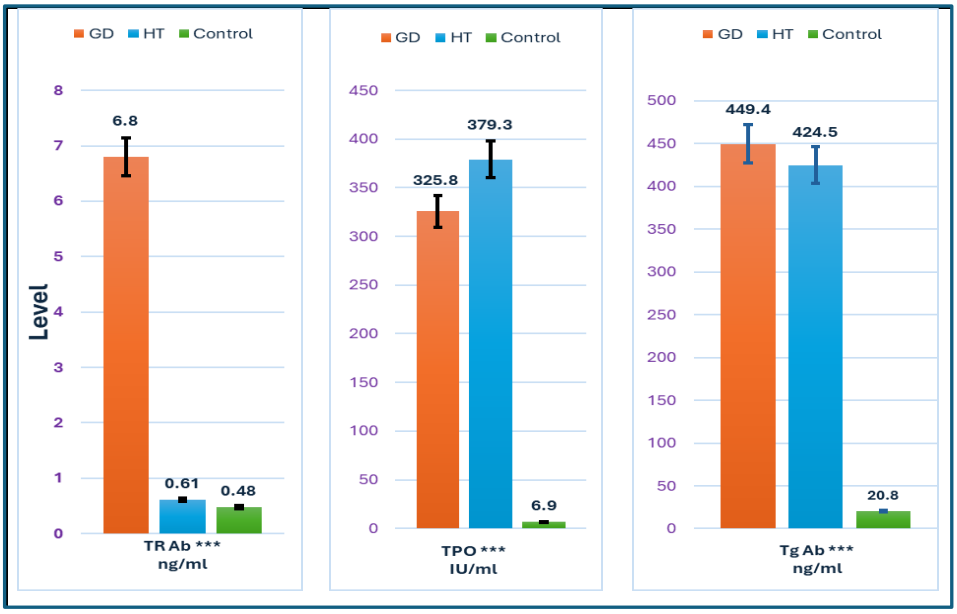

Fig 2: Serum level of thyroid autoantibodies among studied groups. GD: Graves' disease**, HT:** Hashimoto thyroiditis**, TR Ab:** thyroid receptor antibody**, TPO:** thyroperoxidase antibody, **Tg Ab:** Thyroglobulin antibodies, ***:** Very high significant.

Measurement of Cytokine level:

Figure (3) illustrated that cytokine IL27 and IL-1β level are elevated significantly in both GD (higher IL27 level) and HT (higher IL-1β level) when compared to control.

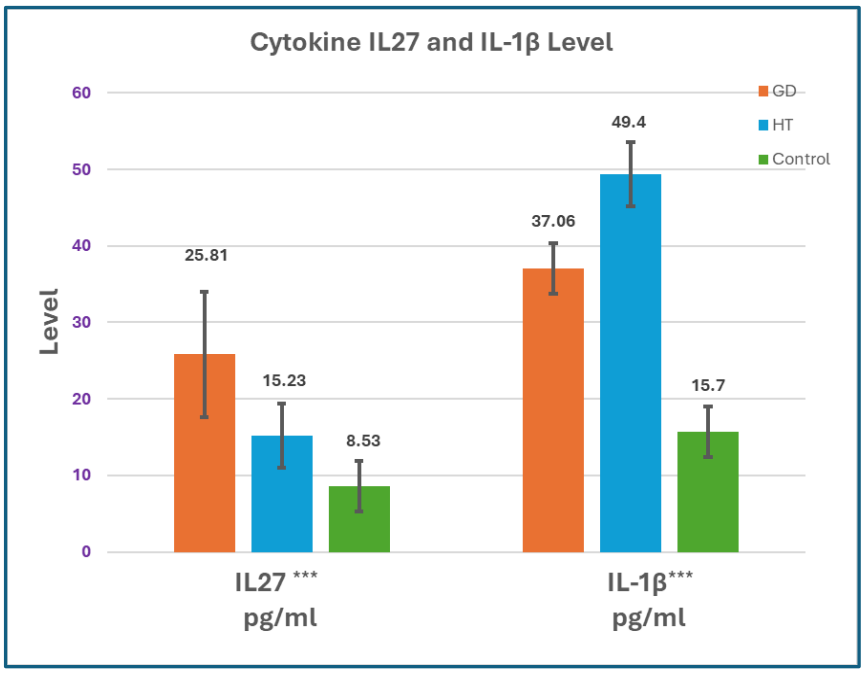

Fig 3: The level of IL27 and IL-1β cytokines among studied groups. GD: Graves' disease**, HT:** Hashimoto thyroiditis**,** IL27: Interleukin 27, IL-1β: Interleukin 1 beta, ***:** Very high significant.

Correlation of IL27 and IL-1β with thyroid hormones in Graves' disease:

The statistical analysis shows that IL27 has weak positive correlation with fT3 and fT4 and weak negative relation with TSH, while IL-1β has weak negative relation with fT3, fT4 and TSH in GD, Figure (4).

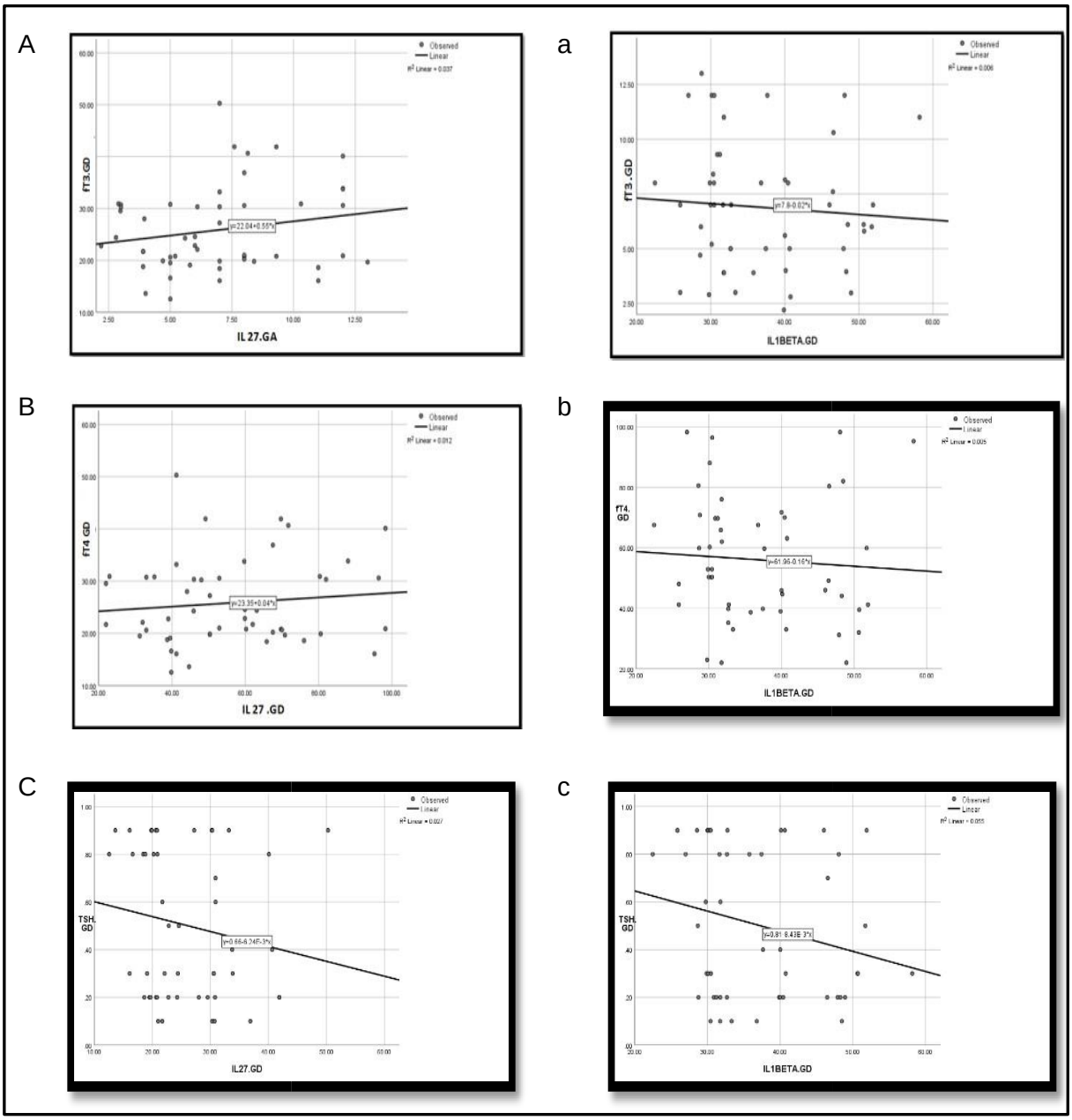

Fig 4: Correlation of IL27 and IL-1β with Thyroid hormones in Graves' disease. A (a): correlation between IL27 (IL-1β) and fT3, **B (b)**: correlation between IL27 (IL-1β) and fT4, **C (c)**: correlation between IL27 (IL-1β) and TSH. GD: Graves' disease, IL27: Interleukin 27, IL-1β: Interleukin 1 beta, fT3: free triiodothyronine hormone, fT4: free thyroxine hormone, TSH: Thyroid stimulating hormone.

Correlation of IL27 and IL-1β with autoantibodies in Graves' disease:

The R^2 test, Figure (5), shows that IL27 has weak positive relation with TR Ab and TPO Ab and week negative relation with Tg Ab, while IL-1β reveals weak negative correlation with TR Ab, TPO Ab, and Tg Ab in GD.

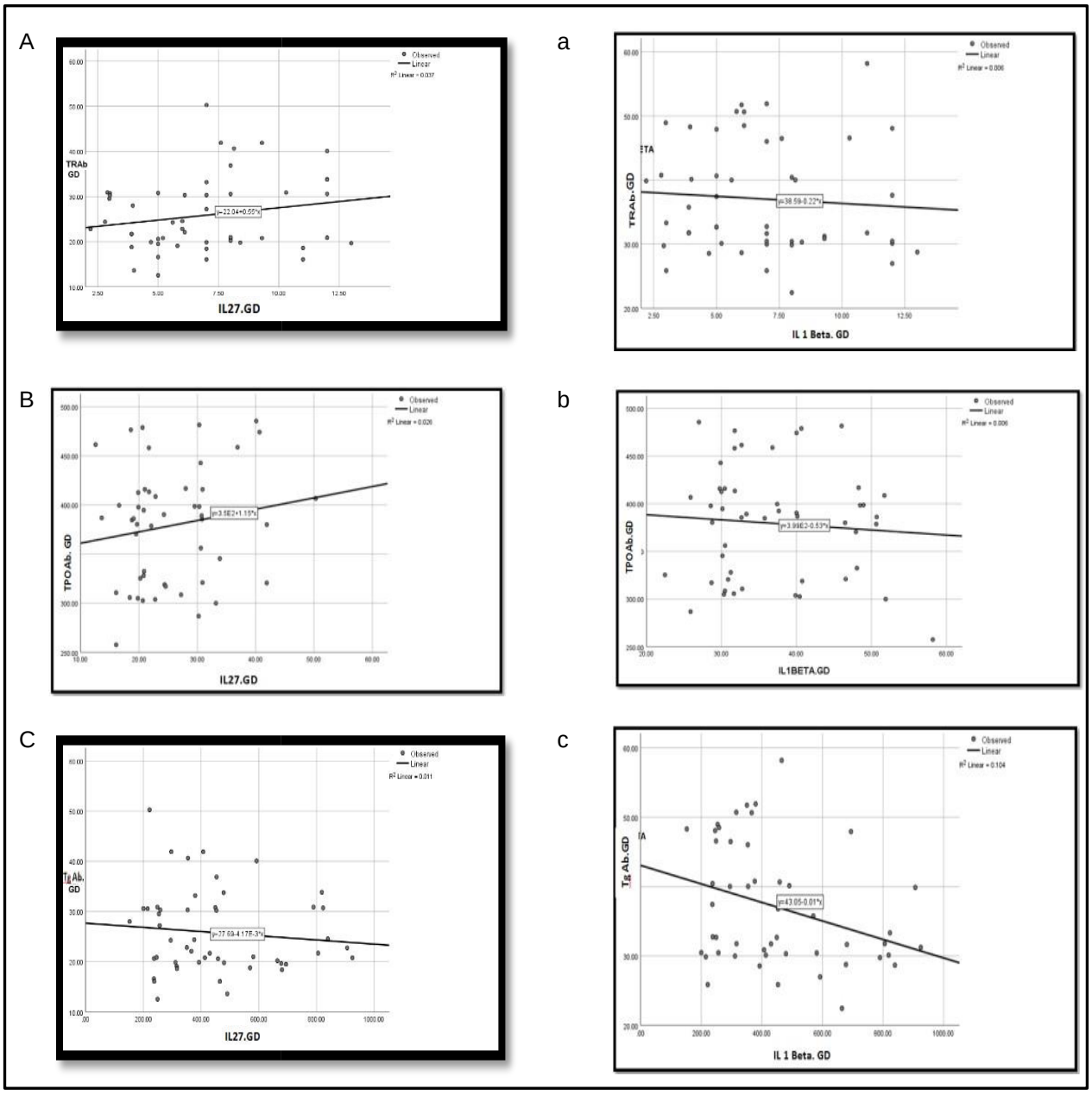

Fig 5: Correlation of IL27 and IL-1β with autoantibodies in Graves' disease. A **(a)**: correlation between IL27 (IL-1β) and TR Ab, **B (b)**: correlation between IL27 (IL1β) and TPO Ab, **C (c)**: correlation between IL27 (IL-1β) and Tg Ab. Graves' disease; IL27: Interleukin 27, IL-1β: Interleukin 1 beta, TR Ab: thyroid receptor antibody; TPO Ab: thyroperoxidase antibody, Tg Ab: Thyroglobulin antibodies.

Correlation of IL27 and IL-1β with thyroid hormones in Hashimoto thyroiditis:

The statistical analysis, Figure (6), shows that IL27 has weak positive link with TSH and weak negative relation with fT3 and fT4, while IL-1β appear in weak positive correlation with fT3 and weak negative relation with fT3 and in HT.

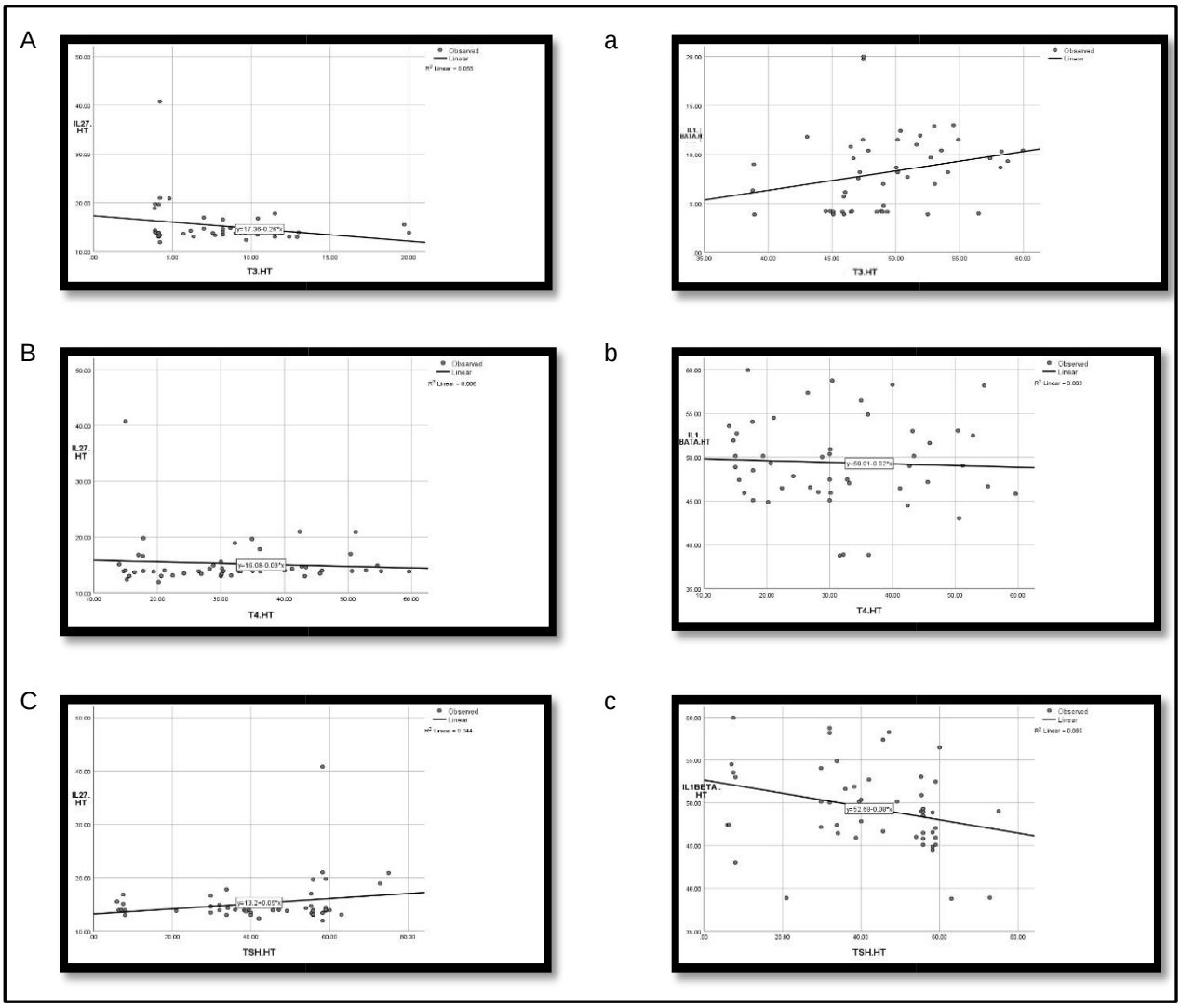

Fig 6: Correlation of IL27 and IL-1β with thyroid hormones in Hashimoto thyroiditis. A (a): correlation between IL27 (IL-1β) and fT3, **B (b)**: correlation between IL27 (IL-1β) and fT4, **C (c)**: correlation between IL27 (IL-1β) and TSH. HT: Hashimoto thyroiditis, IL27: Interleukin 27; IL-1β: Interleukin 1 beta, fT3: free triiodothyronine hormone fT4: free thyroxine hormone, TSH: Thyroid stimulating hormone.

Correlation of IL27 and IL-1β with autoantibodies in Hashimoto thyroiditis:

The linear correlation shows that IL27 has weak positive correlation with TR Ab, TPO Ab and Tg Ab, while IL-1β shows weak positive relation with TR Ab and weak negative link with TPO Ab and Tg Ab in HT, Figure (7).

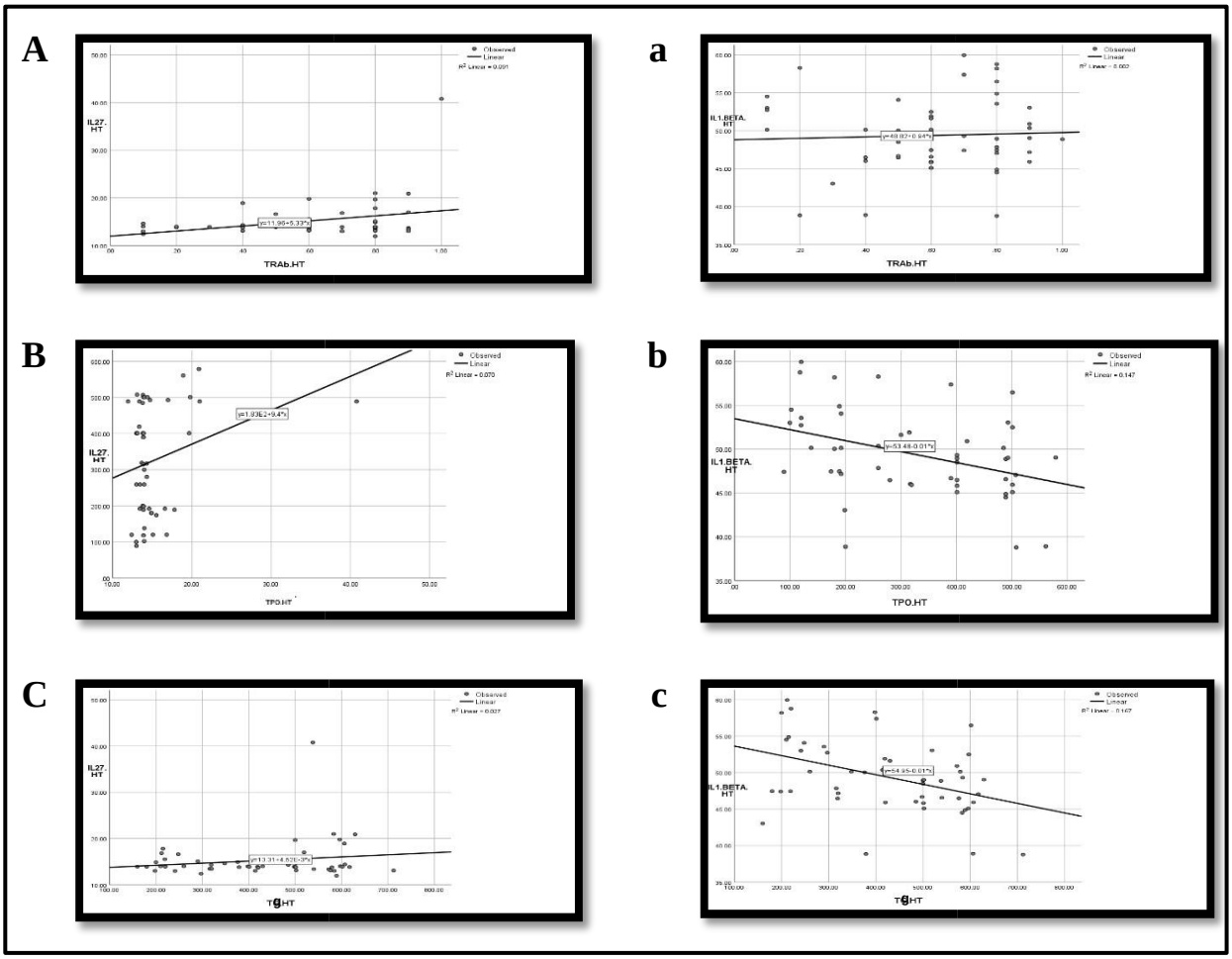

Fig 7: Correlation between IL27 and IL-1β with autoantibodies in Hashimoto thyroiditis. A (a): correlation between IL27 (IL-1β) and TR Ab, **B (b)**: correlation between IL27 (IL-1β) and TPO Ab, **C (c)**: correlation between IL27 (IL-1β) and Tg Ab. HT: Hashimoto thyroiditis, IL27: Interleukin 27, IL-1β: Interleukin 1 beta, TR Ab: thyroid receptor antibody; TPO Ab: thyroperoxidase antibody; Tg Ab: Thyroglobulin antibodies.

DISCUSSION

Based on the results of the current investigation age significantly influenced the prevalence of GD and HT. The age plays a central part in defining the prevalence and incidence of GD and HT, which begins in early adulthood [14]. The majority of GD and HT cases in this study have family history; this result is in agreement with other studies showing that autoimmune thyroid diseases are hereditary. Hereditary contribution has also been associated with the cause of GD and HT with specific genes implicated on the immune system mediation and thyroid hormone synthesis [15,16]. The risk of women as per men of developing autoimmune disease is higher [17]. Hypothyroidism is common throughout the world particularly in women because of instability in feminisms hormones which is shortened in X chromosome and hormone estrogen dominate in females than in males [18]. The current study detects a potential link between abnormal weight and an increased risk of developing GD and/or HT. The obesity can dysregulate adipokines and chronic low-grade inflammation, which can aggravate immune system dysfunction and trigger the emergence of autoimmune diseases such as GD[19]. As well as there is positive association between abnormal body weight and the risk of developing HT [20]. The current study's findings showed that location-related environmental factors have

a major impact on thyroid autoimmunity, as seen by the notable differences in the prevalence of GD and HT between urban and rural populations, this fact is in accordance with results of a study [21], who concluded that hyperthyroidism is higher in rural population. According to a study [22], these factors include exposure to ultraviolet radiation, pollution, pathogenic agents, and iodine ingestion.

The current study defines elevated rates of fT3 and fT4 and decreased rates of TSH in GD, vice versa in HT, this hyperthyroidism and hypothyroidism finding are agreed with result of [23, 24]. These tests facilitate a standard diagnosis of and differentiation between GD and HT. The AIDs induced as a result of humoral (antibody-mediated) and/or cell immunity [25], in the current study, GD and HT had higher levels of autoantibodies TR Ab, Tg Ab, and TPO Ab. The results of current study seem to be in line with those of Al-Mofarji *et al.* [26], who found significant differences in TPO antibody levels between hyperthyroidism patients and healthy individuals. The higher TR Ab levels reported in this investigation are in line with the conclusions made by Fawzi *et al.* [27], whom they found to have higher than normal levels of TR Ab in hyperthyroid individuals. Additionally, a Saudi Arabian study revealed a statistically significant increase in Tg Ab and TPO Ab levels when comparing the hypothyroid and hyperthyroid groups to the control group [28]. Another study done in India discovered that the Tg Ab and TPO Ab levels of female hypothyroid patients were statistically significantly higher levels [29]. Moreover, Al-Mofarji *et al.* [26] detect higher fT3, fT4, TR Ab and TPO Ab levels and reduction of TSH level in hyperthyroidism Iraqi patient. However, there is coexisted of disturbance in thyroid hormone and autoantibodies [30]. Given that cytokines govern both the initiation and the effector phases of all inflammatory as well as immunological responses they are a sine qua non for autoimmunity [31]. The component IL27, which is an indication of proinflammatory cytokines, is fundamental in the transcription and regulation of the T cells, and hence, there relationship between GD and the uncontrollable activation of the T cells [32]. IL-27 is at the moment being considered in the therapy of autoimmune disorders because of its capacity to possess both positive and negative bioactivities [33]. Thus, change of the Th1 to Th2 ratio by the influence of IL-27 may be responsible for non-dominant manifestation of Graves' sickness [34].

Regarding IL-1β could play a crucial part for develop thyroid autoimmunity, Hence, several research, have associated AITD with increased IL-1β levels, implicating the role of this protein in the initiation of HT and GD disease[35,36]. Also, as IL-1β has been related to the synthesis of thyroid hormones and to the stimulation of thyroid follicular cells [45]. Interleukin 1 β commonly referred to as IL-1β, is a major mediator of inflammation and is involved in the regulation of thyroid hormone synthesis in the thyroid gland as well as the activation of immune cells in the body [37]. Therefore, the fact that the patient with AITDs has high levels of IL-1β could be considered as the biomarker that should to be used to monitor the progression and the severity of the conditions. It would be desirable for clinicians to closely monitor the development of the illness and patient's reaction to IL-1β treatment [38]. The current study found relation between IL27 and studied parameters: mostly positive correlation in GD (fT3, fT4, TR Ab, TPO Ab) and in HT (TSH TR Ab, TPO Ab and Tg Ab); and negative correlation with few parameters in GD (TSH, Tg Ab) and in HT (fT3, fT4). While this study detects negative relation between IL-1β and most studied parameters in GD (thyroid stimulating hormone (TSH), free thyroxine (fT4), TSH (thyrotropin) receptor antibody (TR Ab), thyroperoxidase antibodies (TPO Ab), thyroglobulin antibodies (Tg Ab)), and in hyperthyroidism HT: fT3, TPO Ab and Tg Ab; and significant positive correlation with few parameters including fT3, TSH and TR Ab. Due to time constraints, IL27 is in a positive relation and IL-1β in a negative relation with most tests, IL-1β and IL-27 have shown interesting results in GD and HT. They indicated that the positive of relation IL27 and negative of relation of IL-1β might be due to source and/or type of inflammatory affect (pro-, anti-) of studied cytokine as well as the mechanism of AITD.

The role of IL27 and IL-1β in pathogenesis of AITD, GD and HT, is affected significantly by genetic polymorphism[39,40]. In another study, Song *et al.* [20], detect in Iraqi patients a significant association between the IL-1β polymorphism and hyperthyroidism but without relation to fT3, fT4. Understanding the pathogenesis of AITDs, the anti-thyroid antibodies and the cytokines levels must determine because the mechanisms are strongly related [41]. The report of [42], detect no significant correlation of IL-27 with TR Ab, TPO Ab, and Tg Ab in GD, this finding may be due to reduced level of IL27 of them study. Whereas [43], detect that serum IL-1β has significantly inversely relation with fT3 and no other significant correlations with fT4 and TSH. There are different pathogenic mechanisms for GD and HT, both is mediated by autoantibodies, but presence of cytotoxicity in HT but not in GD is a major difference, this difference may explain the negative or positive relation between studied parameters of cytokines thyroid hormones and autoantibodies [44].

CONCLUSION

The current study's concluded that fT3, fT4, TSH, TR Ab had inverted levels, but TPO Ab and Tg Ab have proportional levels in GD and HT, moreover IL-27 and IL-1β were associated significantly with AITDs and both were in positive relation with TSH in HT and negative relation with TSH in GD. More studies are

required to confirm the correlation of cytokine with AITDs to target them for treatment.

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Author Contributions

All authors contributed to the design and drafting of the article. This article is approved by authors.

Conflicts Of Interest

The authors declare that no conflict of interests exist.

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