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The Role of Interferon (IFN- γ) in thyroid autoimmunity.

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Abstract

This study was conducted at the Diabetes and Endocrines Medical Center / Thi-Qar province south of Iraq, during the period between November 2017 to February 2018 . Hundred and fifty and Iraqi Arab with Autoimmune thyroid disease (114female, 36male) their ages range (>24- 65)years. All patients were selected from Diabetes and Endocrines medical center and primary step for diagnosis of Autoimmune thyroid disease (Thyroid stimulating hormone, Free thyroxin , Free triiodiothyronine, anti-Thyroid peroxides ,anti-Thyroglobulin ,anti-Thyroid stimulating hormone receptor) and the second step involved measurement level interferon gamma. The aims of study to demonstrate the role of Interferon gamma in development Autoimmune thyroid disease . The results reveal that the level of Interferon gamma elevated and it had positive correlation with Thyroid stimulating hormone, Free thyroxin ,anti-Thyroid peroxides and anti-Thyroid stimulating hormone receptor (Autoantibody).We conclude from the study that interferon has been a major contributor in the development of autoimmune diseases.

Keywords: Interferon gamma(IFN-γ), Autoimmunethyroid disorder (AITD).

Introduction:

Autoimmune thyroid diseases (AITD) are one of the most common organ-specific autoimmune disorders, of which Hashimoto's thyroiditis (HT) and Graves' disease (GD) are 2 of the most common clinical expressions. HT is characterized by hypothyroidism that results from the destruction of the thyroid by thyroglobulin-specific T cell-mediated autoimmune response(Caturegli *et al.*,2007). In contrast, GD is characterized by hyperthyroidism due to excessive production of thyroid hormone induced by thyrotropin receptor-specific stimulatory autoantibodies. Cytokines play a crucial role in modulating immune responses that affect the balance between maintenance of self-tolerance and initiation of autoimmunity. Cytokines, including proinflammatory cytokines , are important players in the pathogenesis of the these diseases through multiple ways ,such as regulating inflammation and angiogenesis(Guan *et al.*,2017). However, the role of cytokines is often confusing and is neither independent nor exclusive of other immune mediators(Ganesh *et al.*,2011).IFN-γ is the archetype Th1 cytokine produced by CD4+ Th1 cells, CD8+ T cells, and NK cells. IFN-γ alone or in combination with other inflammatory cytokines induces MHC class I and II on APCs and other cells, and up-regulates the expression of adhesion molecules as well as certain chemokines and chemokine receptors to recruit T cells to the site of inflammation. It also activates macrophages and promotes IgG2A antibody production (Ganesh *et al.*,2011).The IFN-γ receptor consists of the alpha chain (known as IFN-g RI) that bind IFN-γ is and the associated beta chain (IFN-g RII) required for biologic activity(RusandVia,2007). IFNγ is important for Th1 responses because of its effects on Antigen present cells. IFN-γ enhances autoimmunity. IFN-γ activates macrophages and plays a crucial role in bridging innate and adaptive immunity by increasing antigen presentation through the MHC class I and II pathways ,In addition, IFN-γ promotes MHC expression on APCs and enhances NK-cell cytotoxic activity. Increases in serum IFN-γ levels have been correlated with favorable clinical responses to immunotherapy treatments (Steven *et al.*,2017).Interferon (IFN)-g-induce expression of human leucocyte antigen (HLA) class II on thyroid follicular cells in trathyroidal production of cytokines (Ajjan and Weetman,2003). interactions between chemokines and their receptors(Romagnan *et al.*,2002). Interaction between co-stimulatory
molecules and activation and inhibition of apoptosis are important mechanisms in the development of thyroid autoimmunity. The pathophysiological significance of soluble plasma forms of cytokines, chemokines, co-stimulatory molecules and markers of apoptosis still remains unclear(kouki *et al.*,2000; Wang & Baker,2007).
The aims of study to demonstrate the role of Interferon gamma in development Autoimmune thyroid disease.

Material and method:

The study was consisted of 150 patient and 50 healthy control with age (>24-65) year, during the period from November 2017 to February 2018. Five ml of blood was collected from each patient and control , and it left to clot for 1-2 hour at room temperature and then centrifuged at 3000 rpm for 10 minutes ,serum was stored at –20C until was used(Ajjan and Weetman,2003). Tested for the determination of thyroid hormone levels: (FT3, FT4, TSH) using a miniVidas system. (Biomerieux ,France).Thyroid anti-TSH receptor

immunoglobulin (anti-TSH), antithyroperoxidase (anti-TPO) and antithyroglobulin (anti-TG) antibodies were measured in all the samples using electrochemiluminescent "ECL" with Modular Analytics cobas e 411 analyzer (Roche Diagnostics, England). ELISA Kits and ELISA system for the quantitative determination of INF-γ was assay employs (Creative Diagnostics/USA) .

The date statistical analysis was done by using SPSS (version 23) in which include the followings: mean ± SE, While correlation between the data obtained were analyzed by using analysis of variance (ANOVA). The level of significance was ($p < 0.01$).

Result:

The table below explain differentiation among concentration of INF-Ɣ patients compared with control. Non-significant increased INF-Ɣ concentration in patients when compared with the healthy controls Mean± SE [(23.03+4.13) Vs (15.80+7.01) ($p \geq 0.01$)] as in Table (1).

Table (1):Evaluation of INF-gamma level.

INF-γ-Pg/ml	NO	Median	Mean ±SE	P-value
patient	100	3.75	23.03±4.13	0.03
Control	50	1.52	15.80±7.01	0.03

As shown in table (2) level INF- γ was non-significant . Increased in hypothyroid than hyperthyroidism (26.75±5.05 u IU/ml), (15.00±6.20 u IU/ml) ($p \geq 0.01$)respectively.

Table (2): INF-γ-level in the thyroid disorder patients.

Thyroid disorder	INF-γ-(u IU/ml) Mean ± SE	F-test	P-value
Hypothyroidism	26.75±5.05	1.57	0. 0214
Hyperthyroidism	15.00±6.20		

In table (3) found strong correlation and significant between INF- γ-and anti- TPO in hypothyroidism group (0.481,$p \geq 0.013$).also found positive correlation and significant between anti-TPO and anti- TG in (0.460,$p \geq 0.018$) in as significant ($p \geq 0.01$).but not found correlation and significant between INF-γ- and FT4,TSH,Anti-TPO,TG.TSHR.

Table(3): Correlations between parameters in patients Hypothyroidism group:FT4,TSH,anti-TSH,Anti-TPO,Anti-TG,INF- γ.

	INF –γ	anti-TPO	Anti-Tg	Anti-TSHR	TSH	FT4
INF- γ	1					
anti--TPO	0.481 0.013	1				
Anti-Tg	-0.122 0.553	0.460 0.018	1			
Anti-TSHR	-0.004 0.091	0.263 0.195	-0.156 0.447	1		
TSH	-0.004 0.984	-0.013 0.948	0.008 0.969	-0.106 0.606	1	
FT4	-0.280 0.165	0.295 0.144	0.179 0.381	0.293 0.146	0.067 0.746	1

***Correlation is significant at the 0.01 level (P-value).**

In table (4) was found strong correlation and significant between anti- TPO and anti-TG, and also anti-TPO and anti-TG with TSH in respectively (0.506,p≥0.000),(0.146,p≥0.016),(0.331,p≥0.004)) in as significant (p≥0.01).Also not found correlation and significant between INF-γ and anti- TG, anti-TSHR, anti-TPO ,FT4andTSH in (0.460,p≥0.018).

Table(4):Correlations between parameters in patients Hyperthyroidism group: INF-γ,FT4,TSH,anti-TSHR,Anti-TPO,Anti-TG

	INF-γ	Anti-TPO	Anti-Tg	Anti-TSHR	TSH	FT4
INF- γ	1					
Anti- TPO	-0.125 0.289	1				
Anti-Tg	-0.112 0.342	0.506 0.000	1			
Anti - TSHR	-0.092 0.437	0.110 0.349	-0.046 0.700	1		
TSH	-0.039 0.743	0.164 0.016	0.331 0.004	-0.010 0.929	1	
F T4	-0.100 0.397	-0.050 0.674	-0.078 0.511	0.007 0.954	-0.228 0.051	1

***correlation is significant at the 0.01 level (P-value).**

Discussion:

Thyroid disorder is a general term representing several different diseases involving thyroid hormones and the thyroid gland. Thyroid disorders are commonly separated into two major categories, hyperthyroidism and hypothyroidism, depending on whether serum thyroid hormone levels (TSH, FT4 and FT3) are increased or decreased, respectively(Wang *et al.*,2007). Increased levels of IFN-γ- produced by the thyroid infiltrating lymphocytes have been shown to facilitate apoptosis of thyroid follicular cells through caspase activation (Wang *et al.*,2007). IFN-γ- is a cytokine released mainly by certain T cells and natural killer cells. IFN-γ- archetype Th1 cytokine produced by CD4+ Th1 cells, CD8+ T cells, and NK cells. IFN-γ alone or in combination with other inflammatory cytokines induces MHC class I and II on APCs and other cells, and up-regulates the expression of adhesion molecules as well as certain chemokines and chemokine receptors to recruit T cells to the site of inflammation (Ganesh *et al.*,2011).

The result observed that INF- γ is the cytokine most clearly associated with AITD, especially hypothyroidism, despite being neither Th1- nor Th2-dependent .Interferon (IFN)-γ-induced expression of human leucocyte antigen (HLA) class II on thyroid follicular cells intrathyroidal production of cytokines interactions between chemokines and their receptors interactions between co-stimulatory molecules and activation and inhibition of apoptosis are important mechanisms in the development of thyroid autoimmunity and IFN-γ released from the infiltrating lymphocytes may play an important role in causing thyroid dysfunction in patients with various forms of thyroiditis (Jiskra *et al.*,2009). The present study also showed correlation high correlation between(IFN)-γ- and AITD, Phenekos *et al* (2004) found that patients with HT had higher INF- γ levels compared to patients with GD and control. Some study indicate in patients with Hashemoto thyroititis found elevated level of IFN-γ in thyrocytes , what may be responsible for of inflammatory process within thyroid gland ls. (Bossowski *et al.*,2011). Upon initiation of the immune response to Thyroglobulin, thyroid-specific T lymphocytes migrate to the thyroid and through interferon (IFN)-γ- production induce thyrocyte expression of major histocompatibility complex (MHC) class-II molecules. This results in further expansion of autoreactive T cells and the inflammatory response leading to the accumulation of activated CD4+ and CD8+ T cells, B cells, plasma cells, and macrophages in the thyroid. Induction of autoimmune responses is believed to be initiated by an environmental trigger (Ajjan and Weetman,2003*;* Carella *et al.*,2004).

It conclude that elevated level (IFN)-γ- of cytokine in and positive correlation with anti-TPO in the hypothyroidism group suggest their role in initiation and development of immune and inflammatory processes in this disease.

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