Serum Levels Of Proinflammatory Cytokines (Interleukin 6 & Interleukin 15) And Adiponectin In Hashimoto's Thyroiditis With Different Thyroid Function States

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Abstract: Hashimoto's thyroiditis is a localized autoimmune disease which is characterized by an overactive immune response of the body directed against its own tissues causing prolonged inflammation**.** Numerous cytokines have been identified at sites of chronic inflammation such as arthritis, thyroiditis and periodontitis as interleukin 6 and interleukin 15. Adiponectin, adipocyte-derived proteins, have immunoregulatory properties and it controls immune responses and inflammation.This study aimed to determine the levels of adiponectin, interleukin 6 and interleukin 15 in patients sera of Hashimoto's thyroiditis with different thyroid functional states (hypothyroidism, euthyroidism and subclinical hypothyroidism). Subjects and methods: Seventy patients (8 males, 62 females) of newly diagnosed Hashimoto's thyroiditis (HT) in Al-Azhar University Hospitals were selected on the basis of high serum levels of anti-thyroid peroxidase antibody (TPO Ab). The patients were divided according to the thyroid function tests into three groups: Free triiodothyronine (FT3), free tetraiodothyronine (FT4) and thyroid stimulating hormone (TSH). The first group was patients with hypothyroidism (H) (3 males, 25 females with mean age 46.5±6.23) with increased TSH and decreased both FT3 and FT4; the second group was patients with euthyroidism (E) (2 males, 16 females with mean age 48.77±6.56) with normal TSH, FT3 & FT4 and the third group was patients with subclinical hypothyroidism (SH) (3 males, 21 females with mean age 48.95±6.61) with increased TSH and normal both FT3 and FT4. The fourth group is a healthy control group (C) (2 males, 15 females with mean age 49.52±7.55) with matched age, gender and body mass index (BMI) with the patient groups. TPO Ab, FT3, FT4, TSH, adiponectin, IL-6 and IL-15 serum levels were measured in all groups. Obtained results revealed a highly significant increase in the mean serum levels of TPO Ab, IL-6 and IL-15 were detected in each of the three patient groups compared to the control group. A positive correlation between adiponectin and each of BMI and WHR in group II (E) only was detected. Also, a highly positive correlation was found between IL-6 and IL-15 in the patient groups. On conclusion, IL-6 and IL-15 may have a possible role in the pathogenesis of Hashimoto's thyroiditis irrespective to thyroid function states. In contrast, the serum level of adiponectin may have no role in Hashimoto's thyroiditis.

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1. Introduction:

Autoimmune diseases affect 5-10 % of the population and are characterized by an overactive immune response of the body directed against its own tissues causing prolonged inflammation. Endocrine autoimmune diseases include Hashimoto's thyroiditis (HT), Graves' disease and type I diabetes mellitus (Sieminska *et al.*, 2010).

Hashimoto's thyroiditis is the most common organ specific autoimmune disease. It is the commonest cause of primary hypothyroidism. An average of 1 to 1.5 in a 1000 people has that disease. It occurs far more often in women than in men (between 10:1 and 20:1) and is most prevalent between 45 and 65 years of age (Paknys *et al.*, 2009). The original study by Hashimoto indicated a striking increase in the number of lymphoid cells and scattered plasma cells in the thyroid gland (Figueroa-Vega *et al.*, 2010).

Numerous cytokines have been identified at sites of chronic inflammation such as arthritis, thyroiditis and periodontitis. One of these, interleukin-6 (IL-6), is a major mediator of host response to tissue injury and infection (marker of inflammatory status) (Gani *et al*.,2009). Also, there is evidence of overproduction of IL-6 in obesity (Olszanecka-Glinianowicz et al., 2004) and autoimmune diseases such as rheumatoid arthritis (Hirano *et al.*, 1988), systemic lupus erythematosus (Chun *et al.*, 2007), allergic urticaria (Lawlor *et al.*, 1993) and Crohn's disease (Gross *et al.*, 1992). Among thyroid autoimmune diseases, increased IL-6 levels have been observed in Graves' disease (Salvi *et al.*, 1996), subacute thyroiditis, and aminodarone-

induced thyrotoxicosis (Bartalena *et al*., 1994). IL-6 regulates growth and differentiation of thyroid cells and its expression in thyreocytes correlates positively with the degree of lymphocyte infilteration (Rugerri *et al*., 2006). IL-6 plays a major role in B cell differentiation and also enhances T cell proliferation and bone resorption. There is a significant correlation between tissue levels of IL-6 and the severity of the coincident inflammation. IL-6 is a 26-kDa glycopeptide whose gene is found on chromosome 7 (Dayer and Choy, 2010).

The cytokine interlukin 15 (IL-15, a protein of 114 amino acids) was first discovered due to IL-2 like stimulatory actions on T cells. The heterotrimeric IL-15 receptor comprises the β and γ chains of the IL-2 receptor with a unique α subunit. These shared receptor subunits most likely explain the similar T cell growth factor properties of both IL-2 and IL-15 (Van Heel, 2006). Several cell types can produce IL-15 including macrophages, keratinocytes, muscle cells, dendritic cells, endothelial cells and neural cells (Bigalke *et al*., 2009). IL-15 has a number of activities including recruitment and activation of T cells, maintenance of T cell memory, stimulation of proliferation and immunoglobulin synthesis by B cells, natural killer (NK) cell proliferation, activation of neutrophils and inhibition of apoptosis (Quinn *et al*., 2009).

There is evidence for crosstalk between adipose tissue and the immune system. Proper production of adipocytokines is needed to keep optimal immune responses. Overnutrition has been found to increase the risk of autoimmune diseases and, conversely, undernutrition has been associated with impairment of cell-mediated immunity (Otero *et al*., 2006).

Leptin and adiponectin, adipocyte-derived proteins,have immunoregulatory properties and they control immune responses and inflammation. These adipocytokines play an important role in the pathogenesis of several autoimmune diseases such as rheumatoid arthritis, type 1 autoimmune hepatitis, lupus erythematosus, type 1 diabetes mellitus and autoimmune encephalomyelitis (Durazzo *et al*., 2009). However, very little is known about adipocytokines production in autoimmune thyroid diseases (Lago, 2007). Sieminska *et al*., 2008 have previously found elevated levels of adiponectin in Graves' disease, and hyperadiponectinemia was related to hyperthyroidism and to TSH-receptor antibodies.

The aim of the present study was to determine the levels of adiponectin, interleukin 6 and interleukin 15 in sera of patients with Hashimoto's thyroiditis with different thyroid functional states (hypothyroidism, euthyroidism and subclinical hypothyroidism) to find its possible role in disease pathogenesis.

2. Subjects and Methods

Seventy patients (8 males, 62 females) of newly diagnosed Hashimoto's thyroiditis (HT) in Al-Azhar University Hospital were selected on the basis of high levels of anti-thyroid peroxidase antibody (TPO Ab) in the serum. Diagnosis of the patients was confirmed by typical hypoechogenic pattern on thyroid ultrasound, presence of a firm and symmetrical enlarged thyroid and thyroid biopsy if possible. Exclusion criteria: Patients receiving anti-thyroid drugs or L-thyroxine therapy were excluded. None of the patients had other autoimmune diseases as type 1 diabetes mellitus, rheumatoid arthritis, pernicious anemia or systemic lupus erythematosus.

The subjects involved in this study were divided into four groups. The first group was patients with hypothyroidism (H) (3 males, 25 females with mean age 46.5±6.23) with increased TSH and decreased both FT3 and FT4. The second group was patients with euthyroidism (E) (2 males, 16 females with mean age 48.77±6.56) with normal TSH, FT3 & FT4. The third group was patients with subclinical hypothyroidism (SH) (3 males, 21 females with mean age 48.95±6.61) with increased TSH and normal both FT3 & FT4. The fourth group was apparently healthy subjects as a control group (C) (2 males, 15 females with mean age 49.52±7.55) of matched age, gender and body mass index (BMI) with the patient groups; they had a normal range of TPO Abs, normal physical & ultrasonographic thyroid examination. BMI was calculated as the ratio of weight to the square of height, and waist hip ratio (WHR) was calculated by dividing the circumferences of the waist and hip. Blood samples were collected from the patients on diagnosis and centrifuged. The serum was kept frozen at -70^{o}C until use.

FT3, FT4 and TSH were measured using an automated VIDAS machine (BioMerieux, France), by Enzyme Linked Fluorescent Assay (ELFA). Normal ranges were 2.5-8.3 pmol/L for FT3, 8.0-24.0 pmol/L for FT4 and 0.25-5.0 µIU/ml for TSH.

TPO Ab was measured by commercially available enzyme immunoassay kits (Accu-Bind ELISA Microwells, Monobind Inc, USA) (Portman *et al*., 1985). Values in excess of 40 IU/ml were considered positive for the presence of anti-TPO autoantibodies. Serum level of adiponectin was determined by quantitative sandwich enzyme immunoassay technique from Quantikine Research, USA (Kishore and Reid, 2000). Normal range for adiponectin was 0.86-21.42 µg/ml. Serum level of IL-6 was determined using AviBion Human IL-6 ELISA Kit, Orgenium Laboratories, Finland and according to

the manufacturer's directions its normal range up to 3.12 pg/ml (Allen, 1997). IL-15 determination using Quantikine Research, USA according to the manufacturer's directions by ELISA technique and its normal range up to 3.9 pg/ml (Grabstein, 1994).

Statistical Analysis:

Data was statistically analyzed using SPSS program version 15 for windows (SPSS, Inc., Chicago, IL). The relation between each group from the three patient groups and the control group was done using ANOVA test. Post Hoc test f (LSD) was done to show the mean and SD of each variable. Determination of Pearson's correlation coefficient (r) was used for correlation between quantitative variables. P-value less than 0.05 were considered to have significant difference.

3. Results:

As shown in table (1); a highly significant (<0.001) increase in the mean serum levels of TPO Ab, IL-6 and IL-15 in each of the three patient groups was observed compared to the control group. The serum adiponectin, BMI and WHR showed no statistically significant difference among the groups. Regarding mean serum levels of FT3 and FT4, there was a significant (<0.001) decrease in H group only compared to the control one. A significant (<0.001) increase in the mean serum level of TSH was revealed in both H and SH groups compared to the control group.

As shown in table (2); the correlations between adiponectin & BMI and adiponectin & WHR, were significant (P<0.05) in group II only.

As shown in table (3); There was a significant positive correlation of serum level of IL-6 and IL-15 in the three groups (r= 0.941, 0.826 and 0.719 in group I, II and III respectively with p value <0.001 in the three groups).

Considering the serum level of IL-15 as in table (4), it showed no significant correlation relationship with TPO Ab in group I, II and III. A significant negative correlation was found between IL-15 and FT3 in group I (r=-0.389 & p<0.05) and group III (r=-0.505 & p<0.05). Regarding the correlation between IL-15 and FT4, a significant negative correlation was found (r=-0.538 & p<0.001) in group III only.

Table (1): Clinical and biochemical characteristics in all groups.

	Group I H group (n=28) Mean± SD	**Group II E group (n=18) Mean± SD**	**Group III SH group (n=24) Mean± SD**	**Control group (n=17) Mean± SD**
TPO Ab (IU/ml): P value	128.9±44.1 P1=<0.001*	86.3±18.8 P2=<0.001*	102.5±11.8 P3=<0.001*	22.0±5.9
FT3 (pmol/L): P value	1.9±0.4 P1=<0.001*	4.9±2.0 P2=>0.05	4.7±1.8 P3=>0.05	4.5±1.6
FT4 (pmol/L): P value	6.5±0.9 P1=<0.001*	13.6±5.1 P2=>0.05	13.6±4.9 P3=>0.05	13.1±3.2
TSH (µIU/ml): P value	8.9±1.3 P1=<0.001*	3.2±1.6 P2=>0.05	7.5±2.0 P3=<0.001*	2.7±1.3
Adiponectin (µg/ml): P value	19.4±5.9 P1=>0.05	18.4±3.2 P2=>0.05	18.4±5.6 P3=>0.05	17.6±4.4
IL-6 (pg/ml): P value	5.1±1.2 P1=<0.001*	5.1±1.0 P2=<0.001*	5.0±0.8 P3=<0.001*	1.5±0.7
IL-15 (pg/ml): P value	5.0±1.2 P1=<0.001*	5.3±1.1 P2=<0.001*	5.0±0.8 P3=<0.001*	1.5±0.7
BMI (kg/m^2): P value	25.9±4.9 P1=>0.05	25.6±4.0 P2=>0.05	25.4±3.1 P3=>0.05	24.6±3.8
WHR: P value	0.8±0.0 P1=>0.05	0.8±0.1 P2=>0.05	0.8±0.0 P3=>0.05	0.8±0.2

P1= group I vs. control group. P2= group II vs. control group.
P3= group III vs. control group. P value is highly significant at <0.001*

Table (2): Pearson's correlation between adiponectin and clinical & biochemical parameters in group I, group II and group III:

	Adiponectin serum level (µg/ml)					
	Group I (H) n=28		Group II (E) n=18		Group III (SH) n=24	
	r	P value	r	P value	r	P value
TPO Ab (IU/ml):	0.103	>0.05	-0.114	>0.05	-0.076	>0.05
FT3 (pmol/L):	-0.015	>0.05	0.179	>0.05	-0.046	>0.05
FT4 (pmol/L):	-0.059	>0.05	0.233	>0.05	0.108-	>0.05
TSH (µIU/ml):	-0.205	>0.05	-0.029	>0.05	-0.209	>0.05
BMI (kg/m^2):	0.132	>0.05	-0.600	<0.05*	-0.098	>0.05
WHR:	-0.025	>0.05	0.488	<0.05*	0.241	>0.05
IL-6 (pg/ml):	-0.002	>0.05	-0.031	>0.05	0.119	>0.05
IL-15 (pg/ml):	-0.007	>0.05	-0.018	>0.05	0.100	>0.05

P value is significant at <0.05*

Table (3): Pearson's correlation between IL-6 and biochemical parameters in group I, group II and group III:

	Serum levels of IL-6 (pg/ml)					
	Group I (H) n=28		Group II (E) n=18		Group III (SH) n=24	
	r	P value	r	P value	r	P value
TPO Ab (IU/ml):	-0.298	>0.05	0.06	>0.05	0.292	>0.05
FT3 (pmol/L):	-0.324	>0.05	-0.135	>0.05	-0.240	>0.05
FT4 (pmol/L):	-0.218	>0.05	-0.087	>0.05	-0.219	>0.05
IL-15 (pg/ml):	0.941	<0.001**	0.826	<0.001**	0.719	<0.001**

P value is highly significant at <0.001**

Table (4): Pearson's correlation between IL-15 and biochemical parameters in group I, group II and group III:

	Serum level of IL-15 (pg/ml)					
	Group I (H) n=28		Group II (E) n=18		Group III (SH) n=24	
	r	P value	R	P value	R	P value
TPO Ab (IU/ml):	-0.311	>0.05	-0.012	>0.05	0.207-	>0.05
FT3 (pmol/L):	-0.389	<0.05*	-0.390	>0.05	-0.505	<0.05*
FT4 (pmol/L):	-0.240	>0.05	-0.290	>0.05	-0.538	<0.001**

P value is significant at <0.05*, P value is highly significant at <0.001**

4. Discussion

Hashimoto's thyroiditis is a localized autoimmune disease which is characterized by the production of the antibodies against thyroid auto-antigens and infiltration of cytotoxic T cells in the thyroid gland leading to the destruction of follicles (Tagami *et al.,* 2010). It is originally described as stroma lymphomatosa which is featured as the formation of lymphoid follicles, marked changes in the thyroid epithelial cells, extensive formation of new connective tissue and diffuse infiltration of round cells (Hollowell *et al.,* 2002). The current study aimed to determine the levels of adiponectin, IL-6 and IL-15 in sera of patients with Hashimoto's thyroiditis with different thyroid functional states (hypothyroidism, euthyroidism and subclinical hypothyroidism).

In the current study, a highly significant increase in the mean of serum level of TPO Ab was detected in the patients groups compared to control group as the selection of the patients in this study depended on the presence of high serum level of TPO Ab. Xie *et al.*, (2008) reported that TPO Ab is the hallmark of HT which could be detected in almost 95% of HT patients' sera. Paknys *et al.*, (2009) stated that Hashimoto's thyroiditis and Graves' disease are different expressions of a basically similar autoimmune process and the clinical appearance reflects the spectrum of the immune response in a particular patient. During that response, cytotoxic

autoantibodies, stimulatory autoantibodies, blocking autoantibodies or cell-mediated autoimmunity may be observed. Persons with classic Hashimoto's thyroiditis have serum antibodies reacting with thyroglobulin and thyroid peroxidase. These antibodies (particularly antibodies against thyroid peroxidase) are complement-fixing immunoglobulins and might be cytotoxic. In addition, many patients have cell-mediated immunity directed against thyroid antigens (Umar *et al*., 2010). Also regarding TPO Ab, no significant correlations were found in this study between each of TPO Ab and IL-6 or TPO Ab and IL-15 in H, E or SH groups. This observation agreed with Prummel and Wiersinga, (2005) as they stated that considering the fact that high TPO Ab concentrations correlate with increased frequencies of Th-1 responsible for thyroid damage and the loss of thyroid function, it can be speculated that antibodies influence the level of TSH. However, Nielsen *et al*., (2009) reported that the exact role of antibodies against thyroid peroxidase is unclear but it is likely that they promote the release of a variety cytokines including IL-6, TNF-α and IFN- .

A significant decrease in serum levels of FT3 and FT4 in group I (H) was detected as that group contained patients having HT with hypothyroid functional state. Also, a significant increase in serum level of TSH in groups I and III (H and SH groups). McCanlies *et al*., (1998) defined HT with hypothyroidism by the presence of high titers of TPO Ab or thyroglobulin antibodies, elevated levels of TSH in the absence of medication, a positive medical history and/or a positive clinical examination. While, they defined euthyroid HT as elevated TPO Ab or thyroglobulin antibodies and normal TSH without the positive medical history or clinical examination seen with hypothyroidism. Xie *et al.*, (2008) revealed that patients with HT have a great deal of clinical status; in general, it is an inconvertible process of evolving from euthyroidism to hypothyroidism and the positive TPO Ab increases the probability of developing hypothyroidism but the progression rate of euthyroidism to subclinical and even to overt hypothyroidism is variable and the progression mechanism of HT is still unclear.

Regarding, adiponectin serum level, the current study showed that no statistically significant difference in comparing patient groups with control group. Durazzo *et al.*, (2009), Aprahamian *et al.*, (2009) and Ehling *et al*., (2006) revealed that it is well known that adipocytokines as adiponectin have immunoregulatory functions and their concentrations are elevated in the peripheral circulation of patients with many autoimmune diseases such as type 1 autoimmune hepatitis, rheumatoid arthritis and systemic lupus erythematosus but the detailed mechanisms of adiponectin actions remain unknown. Sieminska *et al*., (2008) mentioned that very little is known about adipocytokines production in autoimmune thyroid diseases although they found elevated levels of adiponectin in Graves' disease and hyperadiponectinemia was related to hyperthyroidism and to TSH-R antibodies. However, the results of the present study agreed with Sieminska *et al.*, (2010) as they revealed that although overproduction of adiponectin is pathologically involved in collagen-induced inflammatory autoimmune diseases, their results showed no difference of serum adiponectin level was observed with regard to the presence of HT. No significant correlation was observed between adiponectin and TSH in the three groups. This is in contrary to Obregon, 2008 who found that TSH receptors have been found on several fat depots and in animal experiments, TSH directly influences adipose tissue and stimulates adipogenesis through these receptors on the surface of adipocytes. These findings suggest that the pathogenesis of autoimmune thyroiditis is different and independent of connections with adipose tissue as the explanation of Sieminska *et al*., (2010).

The correlation study between adiponectin and each of BMI and & WHR, showed no significant correlation either in group H or group SH. These results could be attributed to BMI and WHR in the subjects in this study were in normal range. Arita *et al*., (1999) revealed that in human, adiponectin levels were found paradoxically to be decreased in obese only, compared with normal individuals, making it the only known adipocyte-specific hormone that is down-regulated in obesity.

The current study, reported a significant increase in IL-6 and IL-15 serum levels in the Hashimoto's patient three groups as compared to the control group. Also, a significant positive correlation was found between IL-6 and IL-15 in the three patient groups. Rugerri *et al.*, (2006) and Matsumura *et al.*, (1999) agreed with our results as they stated that different cytokines released by immune cells cause thyroid cell damage and are involved in inflammatory processes. This finding suggests that IL-6 and IL-15 are involved in the development of the disease in the different thyroid function status. Taddei *et al*., (2006) explained that the chronic activation of the immune system due to HT can lead to impaired endothelium dependant vasodilatation and may cause endothelial dysfunction in humans and IL-6 promotes atherogenesis directly by endothelial-dependant mechanisms and indirectly by stimulating hepatic production of C reactive protein. Also regarding IL-15, Bigalke *et al*., (2009) stated that IL-15 is a proinflammatory cytokine that is present in a broad variety of tissues and cells. It

causes a stimulation of T cell and B cell proliferation and activity whereas IL-15 particularly promotes the proliferation and survival of natural killer cells (Bulanova *et al.,* 2001). Natural killer cells are bone marrow-derived granular lymphocytes that, without previous sensitization and restriction by major histocompatibility proteins, are cytotoxic against malignant and virally infected cells (Dunne *et al.,* 2001).

Furthermore, no significant correlation was observed between adiponectin and IL-6 or IL-15. Rovin and Song, (2006) and Sieminska *et al.*, (2010) disagreed with these results as they stated that the adipokine possesses anti-inflammatory properties although recent studies have documented pro-inflammatory and immunomodulatory effects. They explained that adiponectin activates pro-inflammatory transcription factor NF-κB and ERK1/2MAPK and influences immune responses by regulating T cell activation and suppressing B cell development. They added that the interplay between adiponectin and immune cells plays a role in the development of autoimmune diseases, and in these states, adiponectin correlates with increased serum levels of leptin and IL-6. Also Quinn *et al*., (2009) observed that IL-15 is a cytokine that is highly expressed in muscle tissue and it has a relation with the adipokine as it act as a circulating myokine that inhibits adipose tissue deposition. The results in this study might be attributed to the patients who were selected with normal weight and normal BMI.

From the results of the current study, we concluded that, IL-6 and IL-15 serum levels may be involved in the pathogenesis of Hashimoto's thyroiditis whatever thyroid function status; however, serum adiponectin may have no role. Future studies are recommended to find its exact role in disease monitoring.

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