The Egyptian Journal of Hospital Medicine (October 2022) Vol. 89, Page 4457- 4460

Evaluation of Some Pro-Inflammatory Cytokines Level in Sample of Iraqi Patients with Hyperthyroidism

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ABSTRACT

Background: Hyperthyroidism is a serious public concern, due the continuous increase in its prevalence and its impact on the mortality rates. Autoimmune hyperthyroidism is seen as a thyroid gland problem. Pro-inflammatory cytokines are crucial for the growth and development of hyperthyroidism, it was shown that the level of several pro-inflammatory cytokines were higher in the hyperthyroidism patients.

Objective: This work was aimed to assessment the concentration of certain cytokine in hyperthyroid patients.

Materials and Methods: Sixty hyperthyroidism patients and 30 healthy individuals with age range from (30-65) years old were enrolled in this study through their presence at the National Center for Diabetes Treatment and Research in Baghdad through the period from December 2021 to April 2022.Blood samples were collected to evaluate the level of IL-6, IL-18 and TNF- α using ELISA technique. **Results:** Results showed highly significant (P≤0.01) increasew in IL-6, IL-18, and TNF- α levels in comparison with the control groups. Thus, it can be believed that the pro-inflammatory cytokines can play a role in the pathogenicity of hyperthyroidism. **Conclusion:** It can be concluded that the pro- inflammatory cytokines play a major role in the pathogenicity of hyperthyroidism.

Keywords: IL-6, IL-18, Hyperthyroidism, TNF-α, pro-inflammatory cytokines.

INTRODUCTION

Hyperthyroidism is a clinical condition characterized by excessive serum T4 and T3, or both, with suppression of TSH [(1)]. It has multiple etiologies, [(2, 3, 4)]. Typical signs of hyperthyroidism are weight loss despite increased appetite, tachycardia, restlessness, tremor, weakness and heat intolerance [(5)].

Small signaling proteins known as pro-inflammatory cytokines are up-regulated through inflammation because there is essential for starting and fostering inflammatory responses to illnesses [(6)]. Macrophages are primarily responsible for the production of most cytokines. The most notable pro-inflammatory cytokines are Interleukins (IL-1, -6, -8, -12 and-18), interferons like IFN-γ, and tumor necrosis factors like TNF-α [(7)].

Interleukin-6 is the most pro-inflammatory cytokine, and is responsible for numerous physiological processes, including cell division, apoptosis, differentiation, and survival, which are influenced by IL-6. IL-6 has a variety of activities in the immunological, endocrine, neurological, and hematological systems, including inflammation, bone metabolism, and blood pressure regulation [(5)].Therefore it is affecting the function of B lymphocytes, stimulating the body to produce autoantibodies and stimulates the incidence of hyperthyroidism [(8)].

Interleukin-18 is a member of the IL-1 family, has pleiotropic and powerful pro-inflammatory properties that are strictly regulated at the production and extracellular space levels [(9)]. Interleukin-18 plays essential role in response of T helper cell, by its ability to induce IFN- c production in T cells and NK- cells [(10)]. IL-18 is a key immune response regulator that controls both innate and adaptive immune responses and is the cause of immunological-mediated diseases. It is likely one of the elements involved in the pathophysiology of autoimmune disorders [(11)]. Cytokines are elevated in both autoimmune and non-autoimmune hyperthyroidism, which may be related to the long-term effects of an increase in thyroid hormone [(12)].

TNF-α is a protein produced by body cells that plays a significant role in triggering inflammation. TNF encourages inflammation, along with the fever and symptoms (pain, soreness, and edema) that are related to it, in a number of inflammatory conditions [(13, 14)]. It has a key role as an immunological and inflammatory mediator in the pathogenesis, growth, and progression of a number of infectious, autoimmune, neoplastic, and other disorders. TNF- α play critical role in the onset of autoimmune thyroid disease (AITD) as a powerful pro-inflammatory cytokine. Patients with AITD and Graves' ophthalmopathy had thyrocytes and ocular tissues that contained both TNF-α and TNF-α mRNA [(15)].

MATERIAL AND METHODS

Sixty patients (men and women) with hyperthyroidism after being diagnosed by the physician in addition to thirty healthy subjects with the same age range (30 to 65) years old were included in the research through their attendance to National Center for Diabetes Treatment and Research in Baghdad through the period from December 2021 to April 2022. The necessary information were taken from all subjects after taking their permission depending on the letter of college of science Ethics Committee referenced by the number

Received: 11/5/2022
Accepted: 18/7/2022

CSEC/0122/0036 in January 20, 2022. Blood samples were taken from each participant in the study and the serum was separated for determination the level of IL-6, IL-18 and TNF- α by sandwich Enzyme-Linked Immunosorbent Assay (ELISA). The kits were products of PicoKine Company (USA) [16].

Statistical analysis

SAS (2012) program was used to detect the difference factors between studied parameters. T-test was used for comparison of the means at probability level 0.01. The mean ± standard error (SE) was used to express all results [17].

Ethical approval

An approval of this study was obtained from the University of Baghdad Academic and Ethical Committee (Ref.: CSEC/0122/0036). Informed consents from all the guardians of patients were taken. This study was carried out in accordance with the World Medical Association Code of Ethics (Declaration of Helsinki) for studies involving humans.

RESULTS

Table (1) showed the findings of the current study. Highly significant (P≤0.01) elevation in the concentration of interleukin-6 (38.93 ±0.36 Pg/ml) was noted in hyperthyroidism patients compared to the control group (7.93 ±0.26 Pg/ml). Also, a highly significant (P≤0.01) elevation in the concentration of interleukin-18 (281.23 ±5.39 Pg/ml) was noted in patents when compared to the control (40.73 ± 1.86 Pg/ml). The same table demonstrated a highly significant (P≤0.01) elevation in the concentration of TNF-a (18.76 ±0.29 Pg/ml) in hyperthyroidism patients in comparison with the control group (7.35 ±0.35 Pg/ml).

Table (1): Level of IL-6, IL-18 and TNF- α in hyperthyroidism patients and control

Group	Mean ± SE		
	IL-6 (Pg/ml)	IL-18 (Pg/ml)	TNF-α (Pg/ml)
Hyperthyroidism patients	38.93 ±0.36	281.23 ±5.39	18.76 ±0.29
Control	7.93 ±0.26	40.73 ±1.86	7.35 ±0.35
T-test	1.091 **	15.381 **	0.956 **
P-value	0.0001	0.0001	0.0001
** (P≤0.01).			

DISCUSSION

The significant elevation in IL-6 level in the hyperthyroid patients in comparison with the control group is in agreement with the studies of **Salvi *et al.*[18]**, **Senturk *et al.* [19] and Jha *et al.* [20]**, which has focused on this cytokine and reported its important role of it in the development of hyperthyroidism. **Zhou *et al.* [21]** observed that IL- 6 plays an important part in vascular inflammation because it has various biological activities in different target cells. The thyroid gland produces IL-6, which is induced by TSH, IL-1, and maybe TSH receptor antibodies. It has been proposed that in patients with Graves' disease (GD), the degree of the increase may represent the severity of the condition due to higher IL-6 levels in some studies [19].

Salvi *et al.* [18] found that hyperthyroid patients with active Graves' ophthalmopathy had higher serum IL-6 concentrations than those without eye illness. Previous studies have shown that hyperthyroidism, particularly that brought on by Graves' disease and toxic adenoma, is associated with elevated serum IL-6 levels. These elevations have not been constant, and it has remained challenging to distinguish between the thyroid hormones' role in this elevation and that of the autoimmune inflammatory process prevalent in GD [19].

The results are in agreement with **Fallahi *et al.* [12]**, who has shown significant increase in the level of IL-18 in patients with hyperthyroidism. Also **Ferrari *et al.* [22]** results support the current finding.

Previous studies by **De ciuces *et al.* [23]** and **Miyauchi *et al.* [24]** indicated a significant increase in the concentration of IL-18 in the hyperthyroidism state which has agreement with present study. There are studies concluded that the serum IL-18 levels increased in hyperthyroid state, and were decreased after treatment with antithyroidal drugs [25, 26].

They proposed that TSH regulated IL18 synthesis in thyrocytes. TSH has also been shown to increase the production of cytokines by hematopoietic cells, increase the cytotoxicity of NK cells, and stimulate the growth of T cells that are stimulated by mitogens or IL-2.

The results of TNF-α in the current study are in agreement with **Diez *et al.* [27]** which have shown significant increase in the concentration of TNF-α in hyperthyroid patient. Also **Ma *et al.* [28]** results are in agreement with the present results and prove the involvement of TNF-α in the development and progression of hyperthyroidism. Previous study by **Manolova *et al.* [29]** indicated significant increase in the concentration of TNF-α in hyperthyroidism.

Salvi *et al.* [18] hypothesized that thyroid autoimmunity was more likely to be responsible for elevated TNF- α concentrations in hyperthyroid GD patients than IL-6. TNF- α, is involved in the generation and preserving of immune responses. They are believed to be extremely important in autoimmune thyroid illnesses, such as Graves' disease [30].

Tumor necrosis factor -α can impact the development and differentiation of thyroid follicular cells, which can result in aberrant thyroid hormone production and secretion and a thyroid function issue [(31)]. The thyroid follicular cells of both humans and animals have been found to contain two types of unique receptors. The TNF receptors that are soluble are known as soluble TNF receptor 1 (sTNF-R1) and soluble TNF receptor 2 (sTNF-R2). TNF-R1 plays a major role in mediating TNF-α biological activity, while TNF-R2 is utilized for signal transduction [(30)].

Ma *et al.* [(28)] reported that functional gene polymorphisms in TNF-α, IL-1, 4, 6 and IL-10 may impact hyperthyroidism predisposition. The findings of **Anvari *et al.*** [(32)] revealed that the polymorphism in pro-inflammatory cytokines may play a role in GD predisposition.

CONCLUSION

It can be concluded that the pro- inflammatory cytokines play a major role in the pathogenicity of hyperthyroidism.

Conflict of interest: The authors declare no conflict of interest.

Funding sources: The authors have no funding to report.

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