



# Increased interleukin 1 and tumor necrosis factor alpha levels after thyroid surgery

## Tiroid cerrahisi sonrası artmış interlökin 1 ve tümör nekroz faktör alfa düzeyleri

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### ABSTRACT

**Objective:** The aim of this study was to consider levels of the proinflammatory cytokines IL-1 and TNFα after thyroid surgery.

**Material and Methods:** A total of 200 patients who underwent total thyroidectomy enrolled in this study. Drain fluid samples were taken. IL-1 and TNFα results and their relationship with other factors were analyzed.

**Results:** There was a positive correlation between IL-1 and hyperthyroidism ( $r_s=0.614$ ,  $p<0.001$ ), operative time ( $r_s=0.770$ ,  $p<0.001$ ), and excised thyroid volume ( $r_s=0.829$ ,  $p<0.001$ ). Moreover, there was a positive correlation between TNFα and hyperthyroidism ( $r_s=0.430$ ,  $p<0.001$ ), operative time ( $r_s=0.392$ ,  $p<0.001$ ), and excised thyroid volume ( $r_s=0.398$ ,  $p<0.001$ ).

**Conclusion:** The results of this study showed us that the parameters related to increased proinflammatory cytokine levels after thyroid surgery were hyperthyroidism, operative time, and excised thyroid volume, but this increase did not show us any clinical outcomes related to these parameters.

**Key Words:** Total thyroidectomy, IL-1, TNFα, proinflammatory cytokines, thyroid surgery

### ÖZET

**Amaç:** Bu çalışmanın amacı tiroid cerrahisi sonrası proinflatuvar sitokinler olan interlökin 1 (IL-1) ve tümör nekroz faktör alfa (TNFα) değerlerini saptamaktır.

**Gereç ve Yöntemler:** Toplam tiroidektomi yapılan 200 hasta bu çalışmaya dahil edildi. Hastaların dren sıvılarından alınan örneklerde IL-1 ve TNFα düzeyleri bakıldı ve hasta ile ilgili diğer faktörlerle ilişkili olup olmadığı değerlendirildi.

**Bulgular:** Hipertiroidi, cerrahi süresi ve çıkarılan tiroid volümü ile IL-1 düzeyleri arasında pozitif korelasyon saptandı ( $r_s=0.614$ ,  $p<0.001$ ), ( $r_s=0.770$ ,  $p<0.001$ ), ( $r_s=0.829$ ,  $p<0.001$ ). Ayrıca, hipertiroidi, cerrahi süresi ve çıkarılan tiroid volümü ile TNFα düzeyleri arasında da pozitif korelasyon saptandı ( $r_s=0.430$ ,  $p<0.001$ ), ( $r_s=0.392$ ,  $p<0.001$ ) and ( $r_s=0.398$ ,  $p<0.001$ ).

**Sonuç:** Bu çalışmanın sonucu bize artmış proinflatuvar sitokin seviyeleri saptanmış olmasına rağmen bu artmış değerlerin hastaların klinik sonuçları ile ilgili bir farklılığa sebep olmadığını gösterdi.

**Anahtar Kelimeler:** Total tiroidektomi, IL-1, TNFα, proinflatuvar sitokinler, tiroid cerrahisi

### INTRODUCTION

Surgery is one of the primary causes of trauma, which results in stress, inflammation, and acute trauma-related immunosuppression. During the early post-traumatic period, the cardiovascular, neuroendocrine, and respiratory systems work together in order to protect the organism and ensure hemostasis. Cytokines are the key mediators in this response (1, 2).

Cytokines are low-molecular-weight proteins that play a major role in the regulation of immune responses under normal and pathological conditions, including stress, surgery, and inflammation (3). Hormones, acute phase reactants, free radicals, and cytokines, such as interleukin (IL) 1, IL-6, IL-8, IL-10, and tumor necrosis factor alpha (TNFα), play an important role in the response mechanism to trauma. The main cytokines in this response are IL-1 and TNFα. While some cytokines increase after trauma, the remaining decrease, related to the injury type and degree. It has been reported that stress related to acute trauma, inflammation, and tissue hypoxia increases proinflammatory cytokines in the postoperative period (4-6).

Tumor necrosis factor alpha is a proinflammatory cytokine that regulates cell proliferation, differentiation, and apoptosis and induces production of other cytokines (7-9). TNFα is mainly secreted by macrophages and also by a broad variety of other tissues. It is also a potent modulator of the immune response, mediating the induction of adhesion molecules and other cytokines (10).

Interleukin 1 is a general name for two distinct proteins, IL-1α and IL-1β, considered the first of a small family of regulatory and inflammatory cytokines (11). It derives mainly from macrophages. This molecule plays an important role in the regulation of acute inflammation and is also generally thought of as a prototypical proinflammatory cytokine.

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Surgical operations cause some immunological disturbances that cause a generalized state of immunosuppression in the immediate postoperative period. Immunological changes that occur perioperatively are primarily the result of surgical trauma and subsequent neuroendocrine responses. Surgery related acute trauma-induced immunosuppression is associated with increased proinflammatory cytokine levels, such as IL-1, TNF $\alpha$ , IL-6, and TGF $\beta$  (12, 13).

The inflammatory response related to surgery and trauma could be considered a surgical inflammation (4). Surgical inflammation results in tissue injury and wound healing process. The inflammation process starts immediately after surgery. The acute posttraumatic inflammatory response is made up of three overlapping phases (5). The first, or immediate, phase has been referred as the nervous phase, in which pain and contraction in response to injury start the inflammation. The first increased proinflammatory cytokines are IL-1 and TNF $\alpha$ .

The aim of this study was to consider the proinflammatory cytokines IL-1 and TNF $\alpha$  after thyroid surgery. The outcomes of this increase will be examined in further study.

## MATERIALS AND METHODS

Between January 2009 and December 2010, 200 patients who underwent total thyroidectomy due to multinodular goiter (MNG), Graves disease (GD), and multinodular toxic goiter (MNTG) enrolled in this study in Istanbul University, Istanbul Medical Faculty, General Surgery Department. This study was approved by the ethical committee of the Istanbul Medical Faculty. All patients had given informed consent before taking the samples. All patients underwent total thyroidectomy as a routine procedure. In all procedures, we put suction drains in order to control bleeding. On the morning of postoperative day 1, we took drain fluid samples to examine IL-1 and TNF $\alpha$  levels before taking out the drains. IL-1 and TNF $\alpha$  levels of drain samples were measured by ELISA. All patients' demographic data, diagnosis of the primary disease (MNG, GD, and MNTG), type of surgery, operative time, weight of the excised thyroid gland, and pathology results were recorded. Patients with malignant pathology were excluded from the study, because malignancy alone can result in increased cytokine levels. Only patients with benign pathology were statistically analyzed. IL-1 and TNF $\alpha$  results and their relation with the diagnosis of the disease, primary or recurrent disease, total excised thyroid gland weight, surgery time, and additional disease of the patients were examined.

## Statistical Analysis

All information was collected in a database created by using the Statistical Package for the Social Sciences (SPSS, Inc, Chicago, IL, USA) 19.0 program. Spearman correlation test was used for non-parametric data, and Pearson correlation test was used for parametric data. To examine the relation between IL-1 and TNF $\alpha$  levels and the other parameters, Mann-Whitney U-test was used. P value <0.05 was considered significant.

## RESULTS

Two hundred patients with total thyroidectomy and benign pathology were enrolled in the study. The median age of the patients was 50.5 (18-73) years. One hundred seventy-four (87%) patients were women, and 26 (13%) pa-

Table 1. Mean levels of IL-1, TNF $\alpha$ , weight of excised thyroid gland, and surgery time

Factors	
IL-1 pg/mL (mean $\pm$ SD) (min-max)	2113.4 $\pm$ 2409.3 (139-8880)
TNF $\alpha$ pg/mL (mean $\pm$ SD) (min-max)	71.9 $\pm$ 74.7 (4-381)
Weight of excised thyroid gland (gr) (mean $\pm$ SD) (min-max)	90.7 $\pm$ 82.9 (24-420)
Surgery time (minutes) (mean $\pm$ SD) (min-max)	69.6 $\pm$ 32.9 (35-185)
IL-1: interleukin 1; TNF $\alpha$ : tumor necrosis factor alpha; mean $\pm$ SD: mean $\pm$ standard deviation	

tients were men. Mean IL-1 level was 2113.4 $\pm$ 2409.3 pg/mL (139-8880), and mean TNF $\alpha$  level was 71.9 $\pm$ 74.7 pg/mL (4-381) (Table 1). One hundred sixty-six patients (83%) had MNG, 18 (9%) patients had GD, and 16 (8%) patients had MNTG. One hundred ninety-six patients (93.5%) had primary disease and 13 patients (6.5%) had recurrent disease. The mean weight of excised thyroid gland was 90.7 $\pm$ 82.9 grams (24-420), and the mean time of surgery was 69.6 $\pm$ 32.9 minutes (35-185) (Table 1). Twenty-six (13%) patients had additional diseases (diabetes mellitus, HT, coronary artery disease, and others).

## Correlations

There was a positive correlation between IL-1 and hyperthyroidism ( $r_s=0.614$ ,  $p<0.001$ ), operative time ( $r_s=0.770$ ,  $p<0.001$ ), and excised thyroid volume ( $r_s=0.829$ ,  $p<0.001$ ). In addition, there was a positive correlation between TNF $\alpha$  and hyperthyroidism ( $r_s=0.430$ ,  $p<0.001$ ), operative time ( $r_s=0.392$ ,  $p<0.001$ ), and excised thyroid volume ( $r_s=0.398$ ,  $p<0.001$ ) (Figures 1a-c and 2a-c).

## DISCUSSION

Surgery is one of the primary causes of trauma and trauma-related acute stress. In the presence of acute stress, cytokine levels increase in both the peripheral and central nervous systems. The sympathetic nervous system becomes activated, and noradrenaline and corticosteroid levels become increased. After acute stress, peripheral cytokines are released from T cells, and this results in increased proinflammatory cytokine production (6, 14). If trauma-related stress becomes chronic, the activation of the hypothalamic-pituitary-adrenal axis is the key response to stress and plays an essential role in the immune system (15). The increased production of adrenocorticotrophic hormone from the pituitary gland and subsequent release of cortisol from adrenal glands persists for several days after surgical trauma. Increased glucocorticoids suppress cell-mediated immunity and increase expression of a number of anti-inflammatory genes. The chronic stress results in decreased secretion of pro-inflammatory cytokines (IL-1, IL-2, IL-6, IL-11, IL-13, and TNF  $\alpha$ ) (16).

In this study, we have studied IL-1 and TNF $\alpha$  levels in the early postoperative period. For this reason, we found increased levels of cytokines. In our opinion, if we had studied these parameters in postoperative week 1 or the following weeks, we might have found decreased cytokine levels. This was one of the limitations of this study.

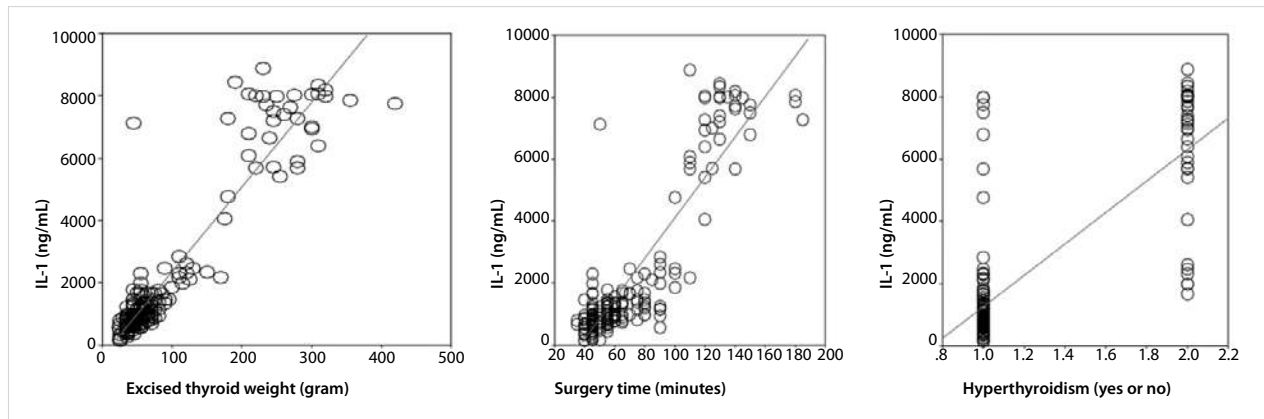


Figure 1. There was a positive correlation between IL-1 and (a) excised thyroid weight, (b) surgery time, and (c) hyperthyroidism

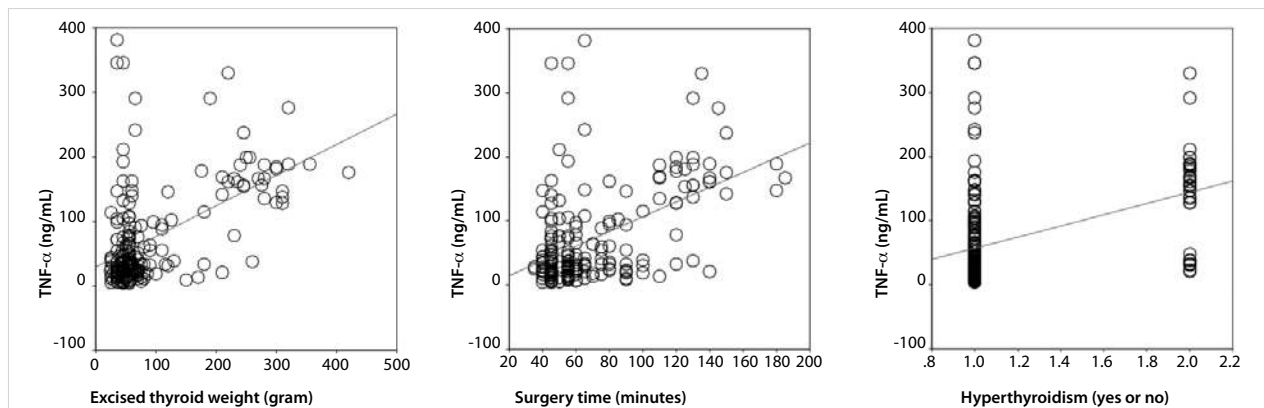


Figure 2. There was a positive correlation between TNFα and (a) excised thyroid weight, (b) surgery time, and (c) hyperthyroidism

Major surgery and severe trauma are also causes of increased proinflammatory cytokine levels. Krohn et al. (17) examined serum and drained blood levels of IL-1 $\beta$ , IL-2, IL-6, IL-10, TNF $\alpha$ , and their modulators after major orthopedic surgery. They examined the levels of these cytokines and modulators early after surgery at the first, second, fourth, and sixth hours. They found increased levels of IL-1 $\beta$  and IL-6 in drained blood and increased TNF $\alpha$  level in serum samples (17). After severe head injury, cytokines are important mediators in the cell-to-cell communication during injury. Cytokines, such as IL-1, IL-6, IL-8, and TNF $\alpha$ , are elevated and play a major role in the cellular cascade of injury. They may have an important role in the pathology of injury, including altered metabolism (18). In the present study, longer operative time (increased trauma and stress level) was found to be related with increased levels of both IL-1 and TNF $\alpha$ . One of the other reasons of the increased level of proinflammatory cytokines after surgery is anesthesia induction and the use of some drugs such as cyclo-oxygenase inhibitors (19).

Surgery-related immunosuppression lasts for 6-9 days after surgery. Immunosuppression after surgery can result in delayed wound healing, respiratory complications, and recurrence after cancer. To reduce the surgery-related immunosuppression, premedication to release stress and anti-inflammatory drugs to reduce pain and prostaglandin E2-induced immunosuppression should be given (20). The development of minimally invasive surgery has limited surgical trauma and related immunosuppression. These also related to reduced postoperative complication rates and shorter hospital stay (6, 21, 22).

Redmond et al. (23) demonstrated significantly increased TNF, chemotaxis, and white blood cell count in open cholecystectomy patients when compared to laparoscopy patients. For these reasons, shorter operative time and hospital stay are important factors after surgery.

Surgical inflammation results in tissue injury and wound healing process. Cytokines and growth factors may have multiple functions that can initiate and influence the wound healing process (24). These factors have the ability to stimulate the release of other cytokines, the promotion of angiogenesis, and production of extra-cellular matrix in the wound healing process after surgery. IL-1 and TNF $\alpha$  have been shown to be essential in the early phases of wound healing (14, 25-27). In this study, we found increased levels of both IL-1 and TNF $\alpha$  on postoperative day 1, in the early phase of wound healing.

Hyperthyroidism is one of the reasons of increased inflammation. Previous studies also showed that thyroid epithelial cells within the thyroid gland secrete TNF $\alpha$ , IL-1, and other proinflammatory cytokines. TNF $\alpha$  can induce the expression of adhesion molecules and regulatory molecules and activates T cells (28-31). There are many studies related to hyperthyroidism and proinflammatory cytokines in the literature, but they have controversial results. Some studies showed increased levels of proinflammatory cytokines in hyperthyroidism, and some did not (32). In this study, we found increased levels of IL-1 and TNF $\alpha$  in previously hyperthyroid patients before surgery.

Hyperthyroidism before surgery, having a larger thyroid volume, and longer operative time have found to be related with increased levels of the proinflammatory cytokines IL-1 and TNF $\alpha$ . These increased levels in patients with hyperthyroidism can be explained by increased inflammation in the hyperthyroid state. The relation with longer operative time can be explained by increased stress and trauma level. Also, large thyroid gland volume and its relation with higher proinflammatory cytokine levels are probably related with increased number of thyroid cells to produce cytokines.

Also, there are several strengths of the present study. It was designed as a prospective clinical study. The study population was large (200 patients were studied), all patients underwent the same procedure, and all operations were performed by the 2 senior surgeons who were trained at the same clinic.

The limitation of this study was that we did not examine the blood levels of proinflammatory cytokines in the study population before surgery to compare with the results after surgery. Moreover, patients' follow-up was not sufficient enough to observe if they would develop complications related to increased levels of proinflammatory cytokines or not.

## CONCLUSION

This study was a prospective, observational clinical study. The results of this study showed us the parameters related with increased proinflammatory cytokines but did not show us any clinical outcomes. We do not know the relationship between increased levels of IL-1 and TNF $\alpha$  and wound complications, wound healing time, or recurrence of the disease in a long follow-up time period. Thus, the relationship between cytokine levels and their clinical outcomes should be examined in further studies.

**Ethics Committee Approval:** Ethics committee approval was received for this study from the ethics committee of İstanbul University İstanbul Faculty of Medicine.

**Informed Consent:** Written informed consent was obtained from patients who participated in this study.

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