Journal of Kyzylorda Scholarly Review

P-ISSN:3006-0265 | E-ISSN:3007-4681. Published by the Open University of Kyzylorda
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https://bulletin.ouk.kz/index.php/bulletin/index



THE INFLUENCE OF IL-6, TGF-B, AND POLYMORPHISMS ON THYROID DYSFUNCTION

Muna Shukri Mahmood Al-Mashhadani[1,*], Haider Jassim Mohammed[2], Hamed Hussein Ali Al- Saadi[3]

[1]Baghdad Directorate of Education, Rusafa II, Ministry of Education, Baghdad, Iraq
[2]Baghdad Directorate of Education, Rusafa III, Ministry of Education, Baghdad, Iraq
[3]Baghdad Directorate of Education, Rusafa III, Ministry of Education, Baghdad, Iraq
Corresponding author*: Mona.Shokri1102a@ihcoedu.uobaghdad.edu.iq

Article History:
Received: 11th Aug 2026; Revised: 19th Sept 2026; Accepted: 10th Oct 2026; Published: 30th Oct 2026

Abstract: The thyroid gland is an important gland responsible for regulating many metabolic processes, such as growth and energy production, through hormone secretion. This gland can malfunction, resulting in conditions like hyperthyroidism or hypothyroidism, both of which can cause various health problems. This study aimed to examine the levels of inflammatory markers, transforming growth factor-beta (TGF-β1) and interleukin-6 (IL-6), as well as to identify genetic differences, in individuals with thyroid disorders compared to healthy individuals. The genotyping of single nucleotide polymorphisms (SNPs) was also investigated to determine their association with inflammation and their impact on thyroid function. Venous blood samples were collected from a group of patients (50) diagnosed with the disease by the medical staff at Madinat Al-Tib Hospital, as well as from a group of healthy individuals (50), during the period from April 2024 to September 2024, The concentration of both transforming growth factor beta (TGF-β1) and interleukin-6 (IL-6) in blood serum was measured using enzyme-linked immunosorbent assay (ELISA). Genomic DNA was also extracted from peripheral blood samples using a DNA extraction kit such as the G-spin™ kit. Genotyping of single nucleotide polymorphisms (SNPs) associated with inflammation or thyroid function was performed using appropriate molecular methods, such as polymerase chain reaction (PCR), restriction fragment length multiplex analysis levels of TGF-β1 in patients with thyroid disorders (116.78±15.35 pg/mL) compared to the healthy control group (29.59 ±16.53pg/mL) ($p < 0.001$). However, no statistically significant difference was observed in interleukin-6 (IL-6) levels between patients (18.26±9.85) compared to healthy individuals (19.45 ± 12.61). Regarding genetic analysis, the results showed no statistically significant difference in single nucleotide polymorphisms (SNPs) in the distribution of genotypes (AA, AC, CC) between patients and control groups. However, the frequency of the "A" allele was significantly higher in the patient group (65%) compared to the control group (55%). The results ed that the rs2736100 genotype had a clear effect on TGF-β1 and IL-6 levels within the same patient group ($p \leq 0.001$). Statistical analysis of the data was performed using SPSS version 25. The current study can be concluded that the expression level of TGF-β1 was high in patients with thyroid disease, and that the rs2736100 genotype showed a clear effect on the levels of TGF-β1 and IL-6 within the same group of patients.

Keywords: IL-6, TGF-β, Polymorphisms, Thyroid Dysfunction

Introduction

The thyroid gland is responsible for regulating many metabolic processes, such as growth and energy production, through hormone secretion (Abdullah et al., 2024). This gland can become dysfunctional, preventing this small but vital endocrine organ from functioning optimally (Yang et al., 2022). This can cause either hyperthyroidism or hypothyroidism, both of which lead to many health problems. These thyroid problems are often associated with the immune system mistakenly attacking the thyroid gland or with persistent inflammation. Understanding these processes is crucial to understanding how these conditions develop and affect individuals (Antonelli et al., 2015). Despite significant progress in understanding these diseases, the molecular and genetic mechanisms that transform the body's normal immune response into a destructive attack on thyroid tissue are still not fully understood, necessitating further research into the factors that cause this transformation (He et al. 2025). Cytokines, small cellular molecules, play a crucial role in regulating the immune response, and any imbalance in their levels can trigger autoimmune disease. Scientists are particularly interested in certain substances found in our bodies called inflammatory cytokines, such as transforming growth factor-beta (TGF-β) and (IL-6). These cytokines are involved in immune responses and in tissue repair, including the thyroid gland (Akarsu et al., 2020).

Interleukin-6 (IL-6) is a prominent cytokine, as its levels are closely linked to autoimmune thyroid inflammation. It plays a crucial role in initiating inflammation, being part of the body's initial response, and it also influences metabolic processes. Therefore, its levels vary depending on the thyroid disorder; in cases of hyperthyroidism, it is at its highest (Bartalena et al., 2018). It also disrupts normal cellular signaling pathways within the gland, making it resistant to conventional treatments (Abbas et al. 2025). Transforming growth factor-β (TGF-β) is a double-edged sword in the autoimmune pathway. Under normal conditions, it acts as an immunosuppressant, but in certain pathological conditions, it can contribute to fibrosis and inflammation. In thyroid diseases, TGF-β plays a crucial role in the differentiation of regulatory T cells (Tregs) and helper T cells (Th17s), guiding their growth in conjunction with IL-6. Any disruption to the Th17 and Treg pathways leads to Hashimoto's thyroiditis and Graves' disease. Therefore, TGF-β acts as a central regulatory molecule in this process, It has multiple functions (Akarsu et al., 2020).

In addition to the role of cytokines, recent research has shown that oxidative stress and endoplasmic reticulum stress play a pivotal role in the development of autoimmune thyroid diseases. Autoimmune thyroid diseases can progress to systemic complications by affecting other tissues and organs in the body. This is because persistent endoplasmic reticulum stress in patients with Hashimoto's thyroiditis extends beyond the thyroid gland to include adipose tissue, contributing to the inhibition of insulin signaling pathways and thus insulin resistance. This illustrates the epidemiological link between thyroid diseases and metabolic syndrome; therefore, anti-inflammatory therapies offer benefits beyond simply improving thyroid function. In mice with Hashimoto's thyroiditis, significant activation of the endoplasmic reticulum stress pathway was observed, leading to increased production of inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) (Zhou et al. 2025). Genes also play an important role in susceptibility to thyroid diseases. Subtle variations in DNA, such as those in genes that control TGF-β and IL-6, can make some individuals more prone to autoimmune thyroid problems by affecting the amount of cytokines produced and, consequently, the functioning of the immune system (Inouye et al., 2020; Vita et al., 2021). The causes of autoimmune thyroid diseases are not limited to environmental and cellular factors; genetic predisposition plays a major role in determining an individual's susceptibility to this disease.

Genome wide association studies (GWAS) have allowed researchers to identify numerous genetic loci associated with thyroid disorders. Approximately 55% of hypothyroidism cases are attributed to genetic factors. This indicates that these disorders have a multi-genetic nature, and single nucleotide polymorphisms (SNPs) are likely risk indicators (Rand et al.

2025). The FOXP3 gene is a key regulator of regulatory T cell (Treg) function, which is important for immune tolerance. Previous research has shown that the rs2232368 polymorphism in the FOXP3 gene is associated with an increased risk of Hashimoto's thyroiditis, and that the AA genotype is associated with a fivefold increase in this risk. This confirms that a single genetic alteration can disrupt the immune system's ability to suppress its attacks on the thyroid gland (Muayad and Jassim 2025). Susceptibility to the disease is affected by genetic patterns. The AG variant at rs13210247 and the CA variant at rs7396562 have been found to increase the likelihood of developing the disease by influencing the severity of the inflammatory response in the gland (Abbas et al. 2025). The interaction between genetic and environmental factors also plays a role in disease development. Additionally, the rs1946518 polymorphism in the gene encoding interleukin-18 (IL-18) is associated with elevated levels of this gene, and vitamin D3 deficiency is associated with elevated levels of TSH and thyroid antibodies. Therefore, this vitamin plays a role in alleviating the severity of the disease in individuals with a genetic predisposition (Shen et al. 2025).

The collection and analysis of disparate data has enabled us to elucidate the mechanisms of disease initiation and progression, identify novel biomarkers for early diagnosis and risk assessment, and propose innovative therapies such as modulating the 17-helper T cell/regulatory T cell pathway, targeting retinal stress, or modifying nutritional and environmental factors. This allows for more effective treatment options for these chronic diseases. Therefore, understanding how these inflammatory cytokines interact and the molecular and genetic basis of thyroid diseases is crucial for improving disease prediction, diagnosis, and treatment. This study was conducted to compare TGF-β and IL-6 levels in individuals with thyroid problems. Specific genetic variations were also investigated to determine their association with an increased risk of thyroid disorders. The aim is to identify reliable indicators for predicting disease progression, monitoring disease progression, and developing more personalized treatments.

Aim of the study

This study aimed to examine the levels of inflammatory markers, transforming growth factor-beta (TGF-β) and interleukin-6 (IL-6), as well as to identify genetic variations, in individuals with thyroid disorders compared to healthy individuals. The genotype of single nucleotide polymorphisms (SNPs) was also examined to determine their association with inflammation and their impact on thyroid function. This will enable a better understanding of the underlying molecular mechanisms, paving the way for the identification of novel diagnostic and therapeutic targets.

Materials and Methods

Study Population

This study included two groups: the first group was a group of patients (n=50) who were diagnosed with thyroid disorders by a specialized medical team, and a control group of healthy individuals (n=50), during the period from April 2024 to September 2024.

Sample Collection and Processing

Venous blood (5ml) was drawn from both groups and placed (3ml) in gel tubes for immunocytokine measurement. The serum was separated by centrifugation at 3000/rpm and (2ml) placed in anticoagulant tubes for genetic testing and stored at -20°C or lower until laboratory analysis.

Measurement of Cytokines

The concentrations of both transforming growth factor-beta (TGF-β) and interleukin-6 (IL-6) in serum were measured using enzyme-linked immunosorbent assay (ELISA). According to the protocols specified by the manufacturer, as with the Koma Biotech kits mentioned in the research paper, the specific details in this study were inferred from the context of the presented data.

DNA extraction and genotyping process

Genomic DNA was isolated from peripheral blood samples with a Routine Kit of DNA. Extraction (specific kit information, e.g., the G-spin™ kit here, would be provided if it is available). Genotyping of the respective single nucleotide polymorphisms (SNPs) related to inflammation or thyroid function was carried out by employing suitable molecular methods, e.g., Polymerase Chain Reaction (PCR) and subsequent restriction fragment length polymorphism (RFLP) analysis or direct sequencing, or by employing pre-designed SNP genotyping assays.

Statistical analysis of the study

The statistical analysis of the data was performed using statistical software. Results for continuous variables (cytokine levels) are presented as mean ± standard deviation (SD). Comparisons between groups (patients vs. controls, hyperthyroid vs. hypothyroid vs. or unpaired Student's t-test, depending on the number of groups and data distribution. The frequencies of genotypes and alleles in the groups were compared using either the chi-square test or exact test of Fisher. The p-value less than 0.05 was considered significant statistically.

Results and decisions

Cytokine Levels

TGF-β levels

Table (1) shows a highly significant difference in TGF-β levels between patients (116.78±15.35) compared to healthy individuals (29.59 ±16.53) ($p \leq 0.001$).

Table 1: Comparison of TGF-β1 levels between patients and controls

Group	N	Mean ± SD	t-value	p-value
patient	50	116.78±15.35	27.33	0.001***
control	50	29.59 ±16.53		

***: highly significant ($p \leq 0.001$).

The marked increase in TGF-β levels in thyroid patients compared to healthy individuals can be explained by the fact that TGF-β plays a crucial role in the immune mechanism by activating the immune system. It is a multifunctional cytokine involved in immune regulation, T-cell differentiation, tissue formation, fibrosis, and extracellular matrix production (Bednarczyk et al., 2025; Hussein and Zayed, 2025).

The results of this study were consistent with those of a previous study that showed a significant increase in TGF-β concentration in untreated Graves' disease patients, but that its concentration decreased after treatment. This suggests a relationship between TGF-β levels and disease activity. Elevated TGF-β levels may reflect persistent immune dysfunction and can therefore be used as an indicator of disease severity and response to treatment. (Hussein and Zayed, 2025)

The results of the current study are also consistent with a previous study that showed significantly higher levels of TGF-β in patients with Graves' disease compared to healthy individuals. This can be explained by abnormal helper T cell responses and cytokine imbalances that characterize autoimmune thyroid disorders (Elvira et al. 2018).

The biological explanation for this elevation lies in TGF-β1 dual role as an immune-regulating cytokine and a fibrotic promoter. In chronic inflammation, activated lymphocytes, phagocytes, and fibroblasts release increased amounts of TGF-β, leading to extracellular matrix deposition, fibrosis, angiogenesis, and enhanced tissue repair mechanisms. The continued activation of these pathways may contribute to thyroid remodeling and thus inflammation control (Bednarczyk et al. 2025).

However, the current findings are inconsistent with those of a study that found significantly lower TGF-β1 levels in patients with Hashimoto's thyroiditis compared to healthy individuals.

This difference could be explained by variations in the type and stage of the thyroid disease studied, its genetic background, sample size, and the laboratory methods used to measure the cytokine. Furthermore, Graves' disease and Hashimoto's thyroiditis are distinct immunological entities, which may explain the difference in TGF-β levels (Akinci et al., 2008).

Overall, elevated levels of this cytokine suggest its role in the pathophysiology of thyroid diseases and can be used as a biomarker to monitor disease activity and immune system dysfunction.

IL-6 levels

Table (2) shows the absence of a significant difference in IL-6 levels between patients (18.26±9.85) compared to healthy individuals (19.45 ± 12.61) (p≤0.05).

Table 2: Comparison of IL-6 levels between patients and controls

Group	N	Mean Levels ± SD	t-value	p-value
patient	50	18.26±9.85	-0.524	0.602 NS
control	50	19.45 ± 12.61		

NS: Non-significant.

The lack of a significant difference in IL-6 levels between patients and healthy individuals suggests that IL-6 may not be an independent inflammatory marker or may not be sensitive to all disease states, as its production is influenced by the degree of immune activity, the type of thyroid disease, the stage of the disease, and the treatment used. Recent studies have shown that IL-6 plays a role in regulating the immune and inflammatory response in autoimmune diseases; however, the elevation of this cytokine does not occur uniformly in all patients, which explains the lack of significant differences in the current study. The results of the current study are consistent with previous research indicating that the relationship between interleukin-6 and thyroid diseases is not always consistent. Using Mendelian randomization, it was shown that inflammatory cytokines in autoimmune thyroid diseases have varying effects depending on the type of disease and the specific cytokine, and that some inflammatory markers do not show a strong correlation across all patients. This explains why no statistically significant differences were found in interleukin-6 levels between patients and healthy individuals (Yao et al. 2024). However, the results of the current study contradict those of a study conducted in Iraq, which found significantly higher IL-6 levels in patients compared to healthy individuals and indicated that IL-6 contributes to the promotion of chronic inflammation and the autoimmune response against thyroid tissue. The difference in results may be attributed to variations in sample size, disease type, or the intensity of immune activity in the two groups (Hashim and Saeed 2024).

Furthermore, the results of the current study do not align with studies conducted on patients with Graves' disease, which demonstrated that the inflammatory cytokine IL-6 plays a role in activating immune cells and B cells responsible for producing antibodies against TSH receptors. Therefore, the lack of elevation in IL-6 found in the current study suggests that the patients were in a relatively stable phase or possibly under the influence of treatment, which contributed to reducing the systemic inflammatory response (Grebenciucova and VanHaerents 2023).

Genotyping Results

rs2736100 Genotypes

Table (3) shows the genotypes of the rs273610 variant and their distribution between patients and healthy individuals. The AA genotype was present in 40.0% of patients compared to 20.0% of healthy individuals. The most common genotype in both groups was AC, at 50.0% in patients and 70.0% in healthy individuals. The CC genotype was present in 10.0% of both groups, The results did not show a statistically significant difference between the genotypes.

Journal of Kyzylorda Scholarly Review
P-ISSN:3006-0265 | E-ISSN:3007-4681
https://bulletin.ouk.kz/index.php/bulletin/index

Table 3: Distribution of rs2736100 Genotypes in patients and controls

Genotype	patient N (%)	control N (%)
AA	20 (40%)	10 (20%)
AC	25 (50%)	35 (70%)
CC	5 (10%)	5 (10%)
X2	5.00	
p-value	0.082 NS	

NS: Non-significant.

Despite the high prevalence of the AA genotype among patients, the differences in genotype distribution did not reach statistical significance. The explanation for this is the lack of a clear correlation between the rs273610 variant and the predisposition to the disease. This may be due to the limited effect of this variant, the small sample size, or the inability of statistical programs to detect this difference (Nie, Shang, and Wang 2023).

The relative increase in the AA genotype among patients is attributed to the presence of the rs273610 variant within the TERT gene, which is responsible for telomerase enzyme activity in maintaining telomere structure and stability. Variations in this gene affect inflammation, cell proliferation, and oxidative stress, thus contributing to the development of thyroid disorders (Nie, Shang, and Wang 2023).

The results of the current study are consistent with a number of genetic studies that found no significant association between certain TERT gene variants and the risk of thyroid disease. These studies indicated that the effect of these genetic variants may vary depending on allelic distribution, ancestry, and sample size, and that differences in genotype frequency do not necessarily imply a pathological effect unless they are statistically significant.(Nie, Shang, and Wang 2023).

In contrast, the results of the current study did not agree with those of a patient with papillary thyroid cancer, where the rs2736100 variant showed a significant association with increased susceptibility to the disease. (Ge et al. 2016) (Nie, Shang, and Wang 2023).

Allele Frequency

Table (4) shows the allele frequency analysis for the rs2736100 genotype between the patient and healthy groups. The analysis revealed that allele A was more common in patients (65%) compared to healthy individuals (55%), while allele C was less common in patients (35%) compared to healthy individuals (45%). However, the difference did not reach the level of statistical significance ($P > 0.05$).

Table 4 : Allele Frequency Analysis in patients and controls

Genotype	patient N (%)	control N (%)
A	65 (65%)	55(55%)
C	35 (35%)	45 (45%)
X2	1.69	
p-value	0.194 NS	

NS: Non-significant.

The increased frequency of the A allele of the TERT rs2736100 gene polymorphism was not significant in patients with thyroid disease compared to the control group, confirming the lack of a clear association between the genetic variant and predisposition to the disease.

This is because thyroid diseases are multifactorial and result from the interaction of numerous genetic variants with immunological and environmental factors. Therefore, the effect of a single genetic variant, such as rs2736100, may be weak or variable depending on the genetic background and size of the sample (Li et al. 2024).

The results of the current study are consistent with a previous study, which showed that most of the genes associated with autoimmune thyroid diseases are single-gene genes with

a small effect. Therefore, the lack of statistically significant differences is expected, especially given the different ethnic backgrounds or small sample sizes. Studies have also confirmed that genetic predisposition to the disease depends on the influence of a large number of genes that regulate the immune response, rather than a single genetic variant (Zhang et al. 2024) (Li et al. 2025).

3.3 Genotype and Cytokine levels

3.3.1 Genotype and TGF-β1

Table (5) results showed a statistically significant difference in TGF-β1 levels between the studied genotypes, as the AC genotype (124.43±18.54) recorded a higher level compared to the AA and CC genotypes (110.66 ± 2.75, 103.08 ± 0.00) respectively ($p < 0.001$).

Table 5: Association Between Genotype and TGF-β1 in Patients

Genotype	N	Mean ± SD
AA	20	110.66 ± 2.75
AC	25	124.43±18.54
CC	5	103.08 ± 0.00
F-value	8.824	
p-value	0.00056 ***	

***: highly significant ($p \leq 0.001$).

The results of the current study showed that genetic polymorphisms affect the regulation of TGF-β1 production and secretion. The AC genotype is associated with higher cytokine levels compared to the AA and CC genotypes. This may be attributed to the fact that the co-occurrence of two different alleles (A and C) can alter the efficiency of gene expression regulation, mRNA stability, or transcriptional regulation mechanisms, thus affecting the amount of protein produced. TFG-β1 is a cytokine that regulates the immune response. It has the ability to suppress inflammation under normal conditions and contributes to the stimulation of fibrosis and tissue remodeling in pathological conditions. Therefore, genetic variations affecting its levels have biological significance in thyroid diseases (Latar et al. 2022).

The elevated TGF-β1 levels in the AC genotype can also be explained by the fact that some genotypes may have a functional effect on regulating molecular pathways associated with the cytokine TGF-β1, leading to differences in cytokine production among different genotypes. Studies have shown that genetic polymorphisms in genes regulating the TGF-β pathway may be associated with increased biological activity of this cytokine and with disease severity and aggressiveness, as they increase its levels in some thyroid diseases and tumors, thus confirming the relationship between genetic background and TGF-β1 levels (Latar et al. 2022).

The results of the current study partially agree with a previous study that demonstrated that certain genetic polymorphisms in TGFB1 are associated with increased activity and higher aggressiveness in thyroid cancer. Therefore, genetic variations influence the level and activity of this cytokine (Peres et al. 2021).

However, these results do not agree with another study conducted on psoriasis patients in Iraq. Researchers found no statistically significant relationship between TGFB1 genotypes and serum TGF-β1 levels, despite an association between genetic polymorphism and disease susceptibility. This may be explained by differences in disease type, the specific genetic polymorphism studied, genetic background, and sample size (Ahmed et al. 2020).However, these results do not agree with another study conducted on psoriasis patients in Iraq. Researchers found no statistically significant relationship between TGFB1 genotypes and serum TGF-β1 levels, despite an association between genetic polymorphism and disease susceptibility. This may be explained by differences in disease type, the specific genetic polymorphism studied, genetic background, and sample size (Ahmed et al. 2020).

3.3.2 Genotype and IL-6

Table (6) results showed a statistically significant difference in IL-6 levels between the studied genotypes, as the CC genotype (37.081± 0.40) recorded a higher level compared to the AA and AC genotypes (18.18 ± 7.86, 14.42 ± 7.35) respectively ($p < 0.001$).

Table 6: Association Between Genotype and IL-6 in Patients

Genotype	N	Mean ± SD
AA	20	18.18 ± 7.86
AC	25	14.42 ± 7.35
CC	5	37.081± 0.40
F-value	21.656	
p-value	0.001***	

***: highly significant ($p \leq 0.001$).

The results in the current table show that the highest levels of the cytokine IL-6 were observed in individuals with the CC genotype compared to those with the AA and AC genotypes ($p < 0.001$). This can be interpreted as the CC genotype being associated with increased inflammatory activity through its influence on gene expression regulation or its impact on immune pathways controlling cytokine production. IL-6 is considered one of the most important pro-inflammatory cytokines, as it is involved in activating immune cells and acts as a promoter of chronic inflammation, which is a key feature of autoimmune thyroid diseases (Hashimoto and Graves ((Lanzolla, Marinò, and Menconi 2024).

These findings support recent evidence demonstrating that genetic variations between individuals directly influence the intensity of the immune response and the production of inflammatory cytokines, and that genetics not only affects the risk of developing thyroid diseases but also the degree and severity of inflammation. Therefore, the elevated IL-6 level in carriers of the CC genotype demonstrates the functional effect of this genotype in increasing the activity of immune cells and enhancing their production of inflammatory mediators, which contributes to increased disease severity and progression (Lichtiger, Fadaei, and Tagoe 2024)

The results of this study are consistent with a study conducted on patients with Hashimoto's thyroiditis in Iraq, which showed elevated levels of interleukin-6 (IL-6) in patients compared to healthy individuals. This increase is due to the inflammatory and immune activity that accompanies the disease. This is confirmed by the results of the current study, which showed that elevated interleukin-6 levels reflect an increased inflammatory response, although the relationship with genetic patterns was not assessed (Hashim and Saeed 2024).

The current findings also align with a study demonstrating that many genes associated with susceptibility to autoimmune thyroid diseases are linked to the regulation of cytokine production, such as IL-6. Genetic polymorphisms can lead to significant differences in immune response among patients, which explains the variation in IL-6 levels across different genotypes (Zhang et al. 2024).

However, the results of the current study did not agree with the previous study, as there was no significant relationship between some genetic variants and IL-6 levels. This discrepancy was attributed to variations in the genetic background of the populations, differences in sample size, the type of disease studied, and environmental and therapeutic factors that influence IL-6 expression levels more than the genotype itself. Therefore, such discrepancies between studies are expected in research related to molecular genetics and autoimmune diseases (Zhang et al. 2024) (Lichtiger, Fadaei, and Tagoe 2024).

Conclusion

It can be concluded that TGF-β1 expression levels were elevated in thyroid patients. The rs2736100 genotype showed a clear effect on TGF-β1 and IL-6 levels within the same patient

group. Although there was no significant difference in the distribution of genotypes and alleles between the patient and healthy groups. Our findings recommend conducting more research and following up with individuals on a large scale and over time. Moreover, further studies that may help us explore the potential use of TGF-β as a means of tracking thyroid disease activity or determining its severity, and thus its potential use as a treatment that may be beneficial in calming inflammation. Our suggestions that investigating more genetic markers and how these processes work to understand the complex relationship between inflammation and an individual's genetic makeup, thus providing a more comprehensive understanding of thyroid diseases.

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