

Assessment of Interleukin-37, the IL-37/TNF- α Ratio, and 8-OHdG as Novel Biomarkers of Oxidative Stress in Iraqi Patients with Hypothyroidism

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ABSTRACT: Background: Hypothyroidism is a commonly diagnosed endocrine disorder frequently associated with metabolic disturbances, oxidative stress, and immune dysfunction; growing evidence indicates that inflammation-related cytokines and oxidative DNA damage contribute to disease progression even in patients receiving thyroid hormone replacement therapy. This study aimed to evaluate serum IL-37 and TNF- α and urinary 8-OHdG levels and to assess the diagnostic and monitoring utility of the IL-37/TNF- α ratio by comparing these biomarkers across control, untreated hypothyroid, and post-treatment groups. **Objective:** This study aims to examine the relationship between serum levels of IL-37, 8-OHdG, TNF- α , MDA, and the IL-37/TNF- α ratio in patients with subclinical hypothyroidism. **Methods:** The study included 120 individuals divided into three groups: 30 newly diagnosed untreated patients, 30 patients receiving levothyroxine therapy, and 60 healthy controls. Enzyme-linked immunosorbent assay (ELISA) was used to determine serum concentrations of IL-37, TNF- α , MDA, and 8-OHdG. **Results:** The results revealed that the levels of TNF- α , MDA, and 8-OHdG of the untreated hypothyroid group were significantly higher than those of both the treated and control groups. In contrast, IL-37 levels were significantly decreased, leading to a marked decrease in the IL-37/TNF- α ratio. The results exhibited significant improvement in inflammatory markers, with partial restoration of IL-37 levels and the IL-37/TNF- α ratio for those patients who are receiving levothyroxine therapy. In addition, MDA and 8-OHdG levels remained significantly higher in patients receiving levothyroxine than those observed in healthy controls. **Conclusions:** The findings indicate that, in hypothyroid subjects receiving prolonged hormone therapy, persistent oxidative DNA damage and elevated proinflammatory cytokine levels were observed. Measuring the levels of IL-37, 8-OHdG, and the IL-37/TNF- α ratio may be valuable adjunctive laboratory tests when assessing for inflammatory response, monitoring treatment effectiveness, and facilitating better insight into the underlying pathophysiologic mechanisms associated with subclinical hypothyroidism.

KEYWORDS: Hypothyroidism; Thyroxine; IL-37; 8-OHdG; Oxidative stress

INTRODUCTION

Hypothyroidism (HT) is one of the most prevalent endocrine disorders worldwide, with reported prevalence estimates ranging from 0.3% to 12%, with higher prevalence observed among women and older adults [1]. Women are affected approximately six times more often than men with an underactive thyroid [2]. Numerous symptoms, including extreme exhaustion, memory loss, poor sleep, soreness in the muscles and joints, dry eyes, and amnesia, are frequently reported by patients with HT. While certain symptoms linger even when the patient is euthyroid, others can be alleviated with sufficient thyroid hormone replacement [3]. A complex and overlapping set of feedback systems that function both inside and outside the hypothalamus, pituitary, thyroid gland, and the numerous target organs receiving thyroid hormones across the body regulates thyroid homeostasis

[4], [5]. Triiodothyronine (T3) (20%) and thyroxine (T4) (80%) are released when the anterior pituitary secretes thyroid-stimulating hormone (TSH) in reaction to the hypothalamus' discharge of thyrotropin-releasing hormone (TRH) [6]. Synthesis requires iodide, TSH stimulation, and tyrosine on thyroglobulin. In circulation, T4 converts to T3 via deiodination. Finally, T3 and T4 maintain homeostasis through a negative feedback loop on TSH levels [7]. Low thyroid hormone levels cause hypothyroidism, which has a variety of causes and syndromes. Primary and secondary hypothyroidism are the two main types of hypothyroidism [8].

The thyroid gland is unable to produce enough thyroid hormones in basic hypothyroidism. When the thyroid gland is functioning usually, secondary hypothyroidism, which is less widespread, arises [9]. The symptoms of primary hypothyroidism include elevated blood TSH levels, which are higher than usual, and lower-than-normal blood T4 concentrations [10]. A mild type of hypothyroidism is called subclinical hypothyroidism. TSH levels above the normal range (5–10 mIU/L) and T4 levels within the standard reference range are present in patients with subclinical hypothyroidism [11]. To relieve symptoms and avoid long-term effects, people with hypothyroidism will need thyroxine replacement therapy for the rest of their lives. Synthetic thyroxine (L-T4) given at doses to restore normal TSH levels is the gold standard for treating hypothyroidism. The conversion of L-T4 to T3 is expected to return T3 levels to normal as well.

Although L-T4 monotherapy is effective in relieving symptoms in most patients with hypothyroidism, approximately 15% of them experience residual symptoms of hypothyroidism [12], [13]. Successful thyroid replacement therapy has been documented since George Redmayne Murray's early work in 1891 [14]. Modern clinical understanding has evolved from simple hormone restoration to recognizing hypothyroidism as a complex pro-inflammatory state driven by systemic oxidative stress. Untreated conditions include hypertension, dyslipidemia, infertility, cognitive decline, neuromuscular dysfunction, and comorbidities like obesity, osteoporosis, depression, sleep apnea, and coronary artery disease [15]. In addition to its metabolic effects, hypothyroidism is increasingly recognized as a pro-inflammatory condition associated with increased systemic oxidative stress. Thyroid hormone deficiency impairs antioxidant defenses, leading to the accumulation of reactive oxygen species (ROS) that are steadily produced in living cells on account of metabolic and biochemical reactions and on account of exposure to material, synthetic, and biological factors. Excessive ROS advances tissue damage and never-ending complications [16]. Oxidative stress plays a main function in the pathogenesis of hypothyroidism. Excessive ROS results in lipid peroxidation, ordinarily calculated according to the level of the malondialdehyde (MDA) compound. Malondialdehyde is a compound formed as a result of peroxidation of polyunsaturated fatty acids (PUFAs). It has previously been used as a biomarker for measuring oxidative stress in various organic samples [17], [18]. Significant oxidative DNA damage is primarily represented by a pivotal marker called 8-hydroxy-2'-deoxyguanosine (8-OHdG). It is the most common and stable byproduct of oxidative DNA damage produced by reactive oxygen species [19]. These markers serve as important indicators of oxidative stress and genotoxic stress occurring in the hypothyroid environment and reflect the extent of cellular damage caused by hormonal insufficiency [20], [21].

This oxidative process is closely related to inflammation. By intensifying the inflammatory response, elevated amounts of pro-inflammatory mediators, like tumor necrosis factor-alpha (TNF- α), aid in the advancement of disease [22]. On the other hand, the body reacts to this harm by utilizing anti-inflammatory processes. A recent addition to the IL-1 family, interleukin-37 (IL-37) is a powerful anti-inflammatory cytokine that inhibits excessive innate immune responses [23]. Cellular integrity is reported to depend on the balance between pro-inflammatory cytokines (TNF- α) and anti-inflammatory cytokines (IL-37) [24], a balance that is often disrupted in hypothyroidism. There is ongoing clinical discussion on this therapy's ability to fully restore biological normalcy of oxidative and inflammatory profiles [25]. MDA, 8-OHdG, TNF- α , and IL-37 levels were examined in this study to determine how they related to the degree of hypothyroidism. The effectiveness of levothyroxine replacement treatment in lowering oxidative damage and reestablishing cytokine equilibrium in hypothyroid individuals was also assessed. This study aimed to investigate the relationship between IL-37 and systemic inflammation and oxidative DNA damage in hypothyroidism by measuring serum IL-37 and TNF- α and urinary 8-OHdG; to compare these biomarkers across control, untreated hypothyroid, and treated groups; and to evaluate the IL-37/TNF- α ratio as a potential novel biomarker for disease activity and treatment response.

MATERIALS AND METHODS

Sample Collection and Study Design

This case-control study was conducted at Mustansiriyah University/ College of Science/ Department of Chemistry and Special Center for Endocrinology and Diabetes in Baghdad, Iraq, from September 2025 to March 2026. The study involved 120 participants aged between 20 and 60, classified into three groups: Group 1 included 30 newly diagnosed, untreated patients with TSH levels above 4 mIU/L; Group 2 comprised 30 hypothyroid patients with a documented history of the disease who had been on levothyroxine replacement therapy for at least twelve months; and Group 3 served as a control group of 60 age- and gender-matched healthy individuals demonstrating normal TSH levels and overall good health. All study participants underwent evaluation by qualified medical specialists and were diagnosed with hypothyroidism in accordance with the American Thyroid Association standards. Diagnosis of primary hypothyroidism was established when serum TSH levels exceeded the standard reference range of 0.27–4.2 μ IU/mL in the presence of typical clinical symptoms. This study was approved by the local Ethics Committee of the College of Science, Mustansiriyah University (Approval No. BCSMU/1025/0046C). Written informed consent was obtained from all participants prior to sample collection and enrollment in the study, in accordance with the Declaration of Helsinki.

Exclusion Criteria

Participants were excluded if they had other autoimmune diseases, diabetes mellitus, or were current smokers. In addition, individuals were excluded if they were pregnant, lactating, or had irregular menstrual cycles; had undergone thyroidectomy or neck irradiation; had a history of pituitary disorders; or suffered from chronic comorbidities such as diabetes, cardiovascular disease, renal or hepatic conditions, cancer, or substance reliance. These control subjects had no history of chronic illness, no current dependence on illegal substances, and normal thyroid function (TSH within reference levels).

Sample Analysis

Five milliliters of whole blood were collected from each participant, allowed to clot for 15 minutes, and centrifuged at 3000 rpm for 10 minutes to obtain serum. The serum samples were stored at -20°C before analysis. Each participant underwent a comprehensive assessment, including a review of medical records and a clinical examination. Serum concentrations of IL-37, TNF- α , MDA, and 8-OHdG were determined using the enzyme-linked immunosorbent assay (ELISA) technique. All measurements were performed according to the manufacturer's kit protocols using human ELISA kits supplied by ELK Biotechnology (China): IL-37 (Cat: ELK1343), TNF- α (Cat: ELK1190), MDA (Cat: ELK7832), and 8-OHdG (Cat: ELK10848). Absorbance was measured using a microplate reader at the specified wavelengths. Thyroid function tests, including TSH, T3, and T4, were performed using the Cobas e 411 analyzer with Elecsys reagent kits (TSH (REF: 08429324190), T3 (REF: 09007725190), and T4 (REF: 09007741190)) supplied by Roche Diagnostics (Switzerland), based on the electrochemiluminescence immunoassay (ECLIA) technique.

Statistical Analysis

GraphPad Prism software (version 9.0) and SPSS statistical software (version 22) were used to perform data analysis, and the results were expressed as mean $\pm$ standard deviation (SD). One-way analysis of variance (ANOVA) test was used to compare three groups (control, patients, and treated), followed by Tukey's post-hoc test for multiple comparisons to determine significant differences between specific groups. P-values less than 0.05 ($p < 0.05$) were considered statistically significant.

RESULTS AND DISCUSSION

The mean value $\pm$ SD for the thyroid hormonal profile of the studied groups is illustrated in Table 1. The results showed a significant difference in the hormonal profile among the three studied groups. The newly diagnosed patient group exhibited significantly higher TSH levels (10.82 ± 5.94 μ IU/mL) compared to the control group (2.13 ± 1.03 μ IU/mL), $p < 0.01$. Following levothyroxine therapy, TSH levels in the treated group (2.84 ± 2.44 μ IU/mL) showed a significant reduction, returning to levels statistically comparable to those of the healthy controls, as shown in Figure 1. Regarding thyroid hormones, total T3 levels showed a slight but significant elevation in the treated group (1.69 ± 0.47

Table 1. Serum levels of TSH, T3, and T4 of the three studied groups

Parameters	Control	Patients	treated	Overall P-value	Pairwise comparisons
TSH (μ IU/mL)	2.13 $\pm$ 1.03 ^a	10.82 $\pm$ 5.94 ^b	2.84 $\pm$ 2.44 ^a	0.01	C vs P: 0.01; C vs T: 0.05; P vs T: 0.01
Total T3 (nmol/L)	1.41 $\pm$ 0.35 ^a	1.46 $\pm$ 0.46 ^a	1.69 $\pm$ 0.47 ^b	0.05	C vs P: 0.05; C vs T: 0.05; P vs T: 0.05
Total T4 (nmol/L)	89.49 $\pm$ 16.08 ^a	88.10 $\pm$ 41.47 ^a	82.68 $\pm$ 51.51 ^a	0.05	C vs P: 0.05; C vs T: 0.05; P vs T: 0.05

Note: Different letters (a, b) show significant differences at ($P \leq 0.05$)

nmol/L) compared to others (1.41 $\pm$ 0.35 nmol/L, 1.46 $\pm$ 0.46 nmol/L, respectively), $p < 0.05$, as shown in Figure 2. Notably, a statistically significant increase in total T3 levels was observed in the treated group compared to the other groups. Clinically, this elevation may indicate a mild overdose or over-replacement of levothyroxine in some patients, leading to enhanced peripheral conversion of total T3 to total T4. While total T4 levels remained statistically stable across all groups [patient group 88.10 $\pm$ 41.47 nmol/L; treated group 82.68 $\pm$ 51.51 nmol/L; control 89.49 $\pm$ 16.08 nmol/L], $p > 0.05$, as shown in Figure 3. The relatively high variability in total T4 levels observed in patient and treated groups may reflect biological heterogeneity among individuals in thyroid function and response to treatment rather than analytical inaccuracy.

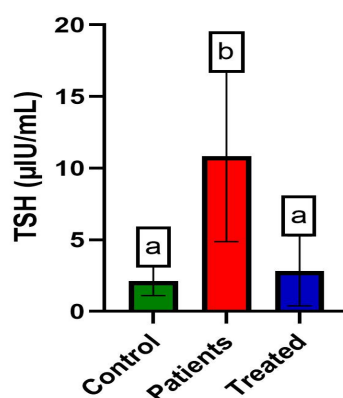


Figure 1. Changes in TSH levels across the study groups. The treated group shows a c towards the control level. Values are signified as Mean $\pm$ SD. Different letters (a, b) show significant differences at ($P \leq 0.01$)

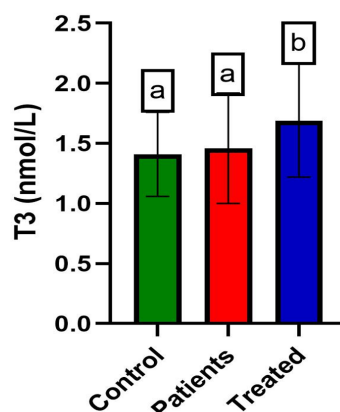


Figure 2. Serum levels of total T3 in control, patients, and treated groups. Bars represent mean $\pm$ SD. Statistical significance is indicated by different superscripts ($P < 0.05$)

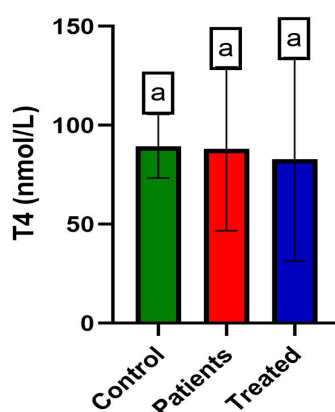


Figure 3. Serum levels of total T4 in control, patients, and treated groups. Bars represent Mean $\pm$ SD

The results also revealed significant alterations in the inflammatory and oxidative status among the three studied groups, as detailed in Table 2. The mean value of the pro-inflammatory cytokine TNF- α was significantly higher in the untreated hypothyroid patient group (228.56 ± 58.49 pg/mL) compared to the control group (104.12 ± 12.92 pg/mL, $P < 0.001$), Figure 4. Conversely, the anti-inflammatory marker IL-37 showed a marked and significant decrease in the patient group (52.08 ± 33.99 pg/mL) relative to the healthy controls (159.08 ± 46.54 pg/mL), Figure 5. Moreover, following levothyroxine treatment, TNF- α and IL-37 markers showed a significant shift toward normal values as in the control.

Furthermore, in the present study, the IL-37/TNF- α ratio was investigated as a novel inflammatory biomarker. The results demonstrated a significant alteration in this ratio among the studied groups, with a marked decrease in patients (0.23) compared to the control group (1.53), followed by a significant increase after treatment (0.71); see Table 2.

Table 2. Serum levels of the inflammatory and oxidative status among the three studied groups

Parameters	Control	Patients	Treated	P-value
TNF- α (pg/mL)	104.12 ± 12.92^a	228.56 ± 58.49^b	137.24 ± 42.23^c	< 0.001
IL-37 (pg/mL)	159.08 ± 46.54^a	52.08 ± 33.99^b	98.12 ± 16.27^c	< 0.001
MDA (nmol/mL)	287.90 ± 70.03^a	1169.63 ± 330.30^b	547.82 ± 232.18^c	< 0.001
8-OHdG (ng/mL)	16.54 ± 3.95^a	75.07 ± 11.82^b	37.45 ± 14.41^c	< 0.001
IL-37/TNF- α	1.53 ± 0.34^a	0.23 ± 0.07^b	0.71 ± 0.19^c	< 0.001

Moreover, the results showed a highly significant elevation in the markers of oxidative damage. The mean level of MDA, a key indicator of lipid peroxidation, was approximately four-fold higher in the patient group (1169.63 ± 330.30 nmol/mL) compared to the control group (287.90 ± 70.03 nmol/mL), Figure 6. This wide variation and high standard deviation for MDA ($SD = 330.30$) in the patient group can be explained by variations in disease duration, age, and clinical presentation among the relatively few. Similarly, the DNA damage marker 8-OHdG exhibited a significant increase in patients (75.07 ± 11.82 ng/mL) compared to controls (16.54 ± 3.95 ng/mL), Figure 7. Although the levels of MDA and 8-OHdG significantly decreased in the treated group compared to the newly diagnosed patients, they remained statistically different from the healthy control levels ($P < 0.05$). This indicates that while the treatment reduces inflammation and oxidative stress, it does not achieve a complete restoration of biochemical levels to baseline levels.

The results of the current study highlight a substantial disturbance in the immune-redox balance of hypothyroid individuals. The crucial result of this study is the imbalance between pro- and anti-inflammatory cytokines, particularly the substantial increase in TNF- α levels and decrease in IL-37. This increase in TNF- α is consistent with a previous study that indicates thyroid hormone depletion activates the NF- κ B signaling pathway systemically [26]. It was reported that when the cell is under oxidative stress, NF- κ B organizes the generation of pro-inflammatory cytokines. Oxidative stress can activate the NF- κ B-dependent inflammatory signaling pathway by increasing the production of ROS.

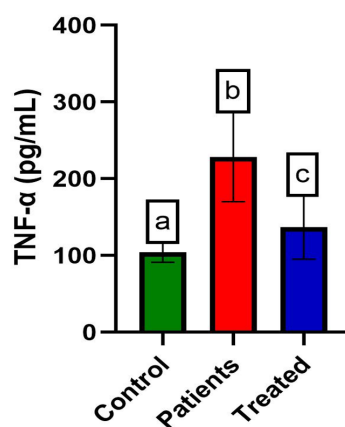


Figure 4. Serum levels of TNF- α in control, patient, and treated groups. Bars represent mean $\pm$ SD. Different letters (a, b, c) indicate significant differences at ($P\leq 0.001$)

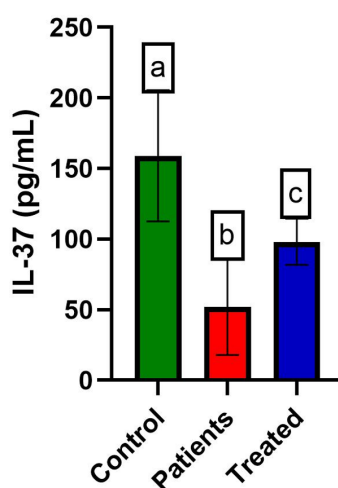


Figure 5. Serum levels of IL-37 in control, patients, and treated groups. Bars represent Mean $\pm$ SD. Different letters (a, b, c) indicate significant differences at ($P\leq 0.001$)

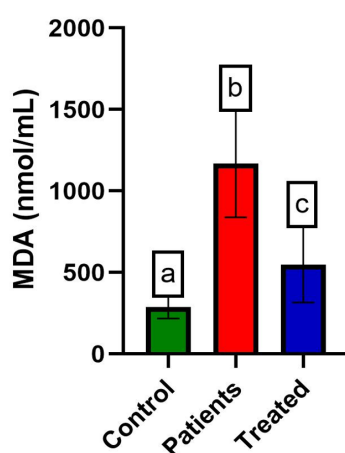


Figure 6. Comparison of oxidative stress marker MDA among study groups. Values are expressed as Mean $\pm$ SD. Different letters (a, b, c) indicate significant differences at ($P\leq 0.001$)

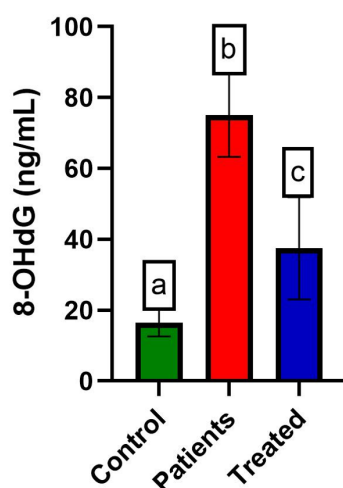


Figure 7. Comparison of 8-OHdG levels among the study groups. Values are expressed as mean $\pm$ SD. Different letters (a, b, and c) indicate statistically significant differences ($P < 0.001$)

This, in turn, stimulates the expression of the inflammatory mediator $\text{TNF-}\alpha$. Consequently, increased $\text{TNF-}\alpha$ production can amplify the inflammatory response, contributing to a positive feedback loop between oxidative stress and inflammation [27]. The substantively decreased levels of IL-37 indicate a new perspective of subclinical hypothyroidism pathophysiology as IL-37 exerts innate immunosuppressive effects via its role in attenuating the production of pro-inflammatory cytokines, inhibiting transcriptional up-regulation of pro-inflammatory cytokines, and inhibiting the stimulation of kinases [28]. A previous study has suggested that IL-37 works as an intermediary modulator of the interface between immunity and metabolism, thereby providing a link between inflammation and thyroid hormone signaling. There is evidence to suggest that disturbances of this regulatory axis result in both inflammatory and metabolic disorders, especially in age-associated metabolic diseases [29], [30]. Due to the significant importance of IL37, a critical anti-inflammatory regulator, the deficiency of IL37 will probably lead to chronic metabolic inflammation. This would keep the immune system in a continuous state of activation. Also, thyroid hormone deficiency would lead to alterations in macrophage immune-metabolic programming to a predominance of the pro-inflammatory M1 phenotype. Macrophages in the M1 state will primarily release pro-inflammatory mediators, which thereby contribute to the development of a chronically inflammatory cycle that has not been adequately addressed through standard clinical treatment aimed only at normalizing thyroid hormones [31].

In this study, the IL-37/ $\text{TNF-}\alpha$ ratio was evaluated as a novel indicator of inflammatory homeostasis. This ratio was significantly lower in patients compared to healthy individuals, suggesting a predominantly inflammatory state. Moreover, this ratio increased significantly after treatment, indicating a partial restoration of immune homeostasis and reinforcing its potential utility as a biomarker of therapeutic response and disease activity. The study found oxidative stress in addition to the inflammatory cascade, which contradicts the widely held belief that a low metabolic rate inherently guards against oxidative stress [32]. However, current biochemical evidence implies that subclinical hypothyroidism results in declined metabolic clearance, a state characterized by the accumulation of metabolic waste due to impaired elimination pathways [33]. The increase in MDA levels reinforces far-reaching lipid peroxidation that compromises the purity of cell membranes and makes cells more susceptible to damage [34]. The mechanisms of antioxidant activity, normally regulated by thyroid hormones, are severely impaired. Elevated 8-OHdG levels indicate genome damage due to oxidative stress [35]. Our results back the emerging theory that DNA damage in hypothyroidism takes place faster than the basic repair system can maintain. Additionally, lipid peroxidation influences the cell sheath, making DNA more susceptible to damage [36], [37]. It is correct that further research is desired to validate this important plan for patients taking it. Levothyroxine treatment resulted in a notable improvement in the evaluated parameters compared to the untreated group; however, none of these markers fully returned to healthy baseline levels. This finding suggests that restoring TSH levels may partially reduce oxidative stress and the inflammatory burden, although hormone replacement alone is insufficient to completely reverse the downstream cellular damage caused by chronic oxidative exposure. Importantly, these variations within the treated group demonstrate that achieving biochemical euthyroidism does not necessarily equate to full physiological recovery. This observation aligns with real-world clinical evidence, indicating that even after TSH levels normal-

ize following levothyroxine therapy, 25–28% of patients continue to experience persistent symptoms, such as fatigue [38]. The limits of levothyroxine monotherapy in a subset of individuals have also been highlighted by systematic studies, which have found that 10–15% of hypothyroid patients still have symptoms even after receiving adequate levothyroxine replacement [39]. It has been reported that levothyroxine treatment reduces oxidative stress and inflammatory indicators from a biochemical standpoint, but these parameters frequently do not return to values similar to those of healthy people [40]. Therefore, the persistence of immunological and oxidative disruptions at the cellular level may offer a tenable explanation for the persistent symptoms seen in certain individuals despite what appears to be sufficient hormonal control.

CONCLUSION

This study demonstrates that subclinical hypothyroidism is a disorder that results in direct DNA damage and systemic inflammation in addition to being a hormone shortage. Our findings indicate that a pronounced decrease in IL37 is linked to persistent oxidative stress and heightened inflammatory activity; moreover, the IL37/TNF ratio discriminated control, patient, and treatment groups, supporting its potential utility as a novel inflammatory biomarker. Most significantly, our findings demonstrate that although levothyroxine treatment effectively restores normal TSH, it is insufficient to totally repair the cellular damage. This is evidenced by the fact that patients' bodies did not fully recover at the cellular level because, even after treatment, their levels of MDA and 8-OHdG remain higher than those of healthy individuals. To ensure that the patient has fully healed, we advise utilizing IL-37 and 8-OHdG as novel indicators and incorporating antioxidants into the conventional treatment.

SUPPLEMENTARY MATERIAL

None.

AUTHOR CONTRIBUTIONS

Asseel Ammar Hammed: Data curation, Investigation, Methodology and Writing – original draft. Falah S. Al-Fartusie: Methodology, Formal analysis, Supervision, Writing, reviewing, and editing.

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DATA AVAILABILITY STATEMENT

Data are available from the authors upon reasonable request.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

DECLARATION OF GENERATIVE AI USE

The authors declare that no generative AI or AI-assisted technologies were used in the preparation of this manuscript.

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