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Exploring the Interplay of TGF-β and Body Weight in Thyroid Cancer: A Comparative Analysis of Cytokine Levels Before and After Surgery in Differentiated Thyroid Cancer and Obese Patients with Nodular Goiter

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Abstract

Introduction: Thyroid cancer and obesity are prevalent conditions with significant global health implications. Differentiated thyroid cancer (DTC) is influenced by various molecular pathways, including those involving Transforming Growth Factor-Beta (TGF-β), a cytokine implicated in cell proliferation, differentiation, immune regulation, and fibrosis. Obesity (BMI > 30) has been associated with thyroid dysfunction and an increased incidence of nodular goiter. However, the relationship between TGF-β levels, thyroid malignancies, and metabolic disturbances remains unclear. This study aimed to analyze TGF-β1, -2, and -3 concentrations in blood serum before and after thyroidectomy in patients with DTC and obese individuals with nodular goiter to evaluate their potential role in thyroid pathology and obesity-related metabolic changes. **Methods:** A prospective study was conducted at a high-volume surgical center where over 700 thyroidectomy procedures are performed annually. Seventy-six consecutive patients (aged 26–79 years) were included: 21 with DTC and 55 with euthyroid nodular goiter. The latter group was subdivided based on BMI into obese (BMI > 30, n = 26) and non-obese (BMI < 30, n = 29) cohorts. Blood samples were collected preoperatively and on the first postoperative day for TGF-β quantification using the Bio-Plex Pro™ Human Cytokine Assay. Statistical analysis was performed using the Student's t-test. **Results:** Postoperatively, patients with DTC exhibited significantly higher TGF-β1 (210,000 pg/mL), TGF-β2 (360 pg/mL), and TGF-β3 (170 pg/mL) levels compared to obese patients with nodular goiter ($p < 0.05$). In the nodular goiter group, BMI did not significantly influence preoperative TGF-β levels ($p > 0.05$). However, postoperatively, obese patients showed lower TGF-β1 (100,000 pg/mL) and TGF-β2 (30 pg/mL) levels compared to normal-weight individuals ($p = 0.03$), while no significant difference was observed for TGF-β3 ($p > 0.05$). **Conclusions:** The study highlights distinct alterations in TGF-β isoform levels in thyroid cancer and obesity. Elevated postoperative TGF-β levels in DTC patients suggest a role in tumor progression and response to surgical intervention. In contrast, the reduction of TGF-β1 and TGF-β2 levels in obese patients postoperatively may indicate a complex interplay between obesity, surgical stress, and cytokine regulation. These findings underscore the need for further research into the molecular mechanisms governing TGF-β dynamics in thyroid disorders and obesity, with potential implications for therapeutic interventions.

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Keywords: TGF-β; thyroid cancer; nodular goiter; obesity; cytokine levels; surgical stress; thyroid pathology; immune modulation; metabolic health; cytokine dynamics; postoperative changes; thyroid disorder; differentiated thyroid cancer; body weight impact; inflammatory response

1. Introduction

Thyroid cancer and obesity are two prevalent conditions with significant global health implications. Differentiated thyroid cancer (DTC), the most common form of thyroid malignancy, is influenced by various molecular pathways, including those involving cytokines and growth factors [1]. Over the past few decades, the incidence of thyroid cancer has been rising, partly due to increased detection and environmental factors, but also potentially linked to metabolic disorders such as obesity [2].

Obesity (BMI > 30) is a well-established risk factor for multiple metabolic and inflammatory disorders, including insulin resistance, type 2 diabetes, and cardiovascular disease [3]. It has also been linked to thyroid dysfunction, an increased incidence of nodular goiter, and a higher likelihood of developing thyroid malignancies [4]. The mechanisms underlying this association are complex and involve chronic low-grade inflammation, alterations in adipokine secretion, and dysregulated cytokine signaling.

Among the key regulators implicated in both thyroid cancer progression and obesity-related inflammation is Transforming Growth Factor-Beta (TGF-β). TGF-β is a multifunctional cytokine that plays a critical role in cell proliferation, differentiation, immune regulation, and fibrosis [4]. It is known to have a dual role in cancer biology: while it acts as a tumor suppressor in early-stage cancers, it promotes tumor progression and metastasis in later stages through epithelial-to-mesenchymal transition (EMT) and immune evasion [5]. In obesity, TGF-β has been implicated in adipose tissue fibrosis and chronic inflammation, contributing to metabolic dysfunction [5].

Emerging evidence suggests that TGF-β may contribute to both tumor progression in thyroid cancer and chronic inflammation associated with obesity. However, the precise relationship between TGF-β levels, thyroid malignancies, and metabolic disturbances remains unclear [6]. In particular, the differential regulation of TGF-β isoforms (TGF-β1, -β2, and -β3) in these conditions has not been fully elucidated [7]. Understanding these relationships is crucial, as TGF-β may serve as a potential biomarker for disease progression or a therapeutic target [8].

This study aims to analyze the concentrations of TGF-β1, -β2, and -β3 in blood serum before and after surgical intervention in patients with DTC and obese individuals with nodular goiter. By comparing these cytokine levels, we seek to elucidate the interplay between thyroid disorders and metabolic health, offering potential insights into the role of TGF-β as a biomarker or therapeutic target in these conditions

2. Material and Methods

The study was conducted at a high-volume surgical center, where more than 700 thyroidectomy procedures are performed annually. Patient recruitment took place over a three-month period, resulting in a total of 76 participants aged 26 to 79 years. Among them, 21 patients were diagnosed with differentiated thyroid cancer, while 55 had euthyroid nodular goiter. The latter group was further stratified based on body mass index (BMI): 26 patients were classified as obese (BMI > 30), and 29 as non-obese (BMI < 30).

Peripheral blood samples were collected from the cubital vein into heparinized vacutainer tubes (10 IU/mL blood) one day before surgery (preoperative) and on the first

postoperative day. Samples were immediately placed in a thermal transport container and delivered to the laboratory for processing. Upon arrival, blood samples were centrifuged at 250× *g* for 10 min at room temperature. The resulting plasma supernatant was carefully transferred into Eppendorf tubes and stored at −80 °C until analysis. All samples were thawed only once, immediately before conducting the Bio-Plex assay. The concentrations of TGF-β1, TGF-β2, and TGF-β3 were measured using the Bio-Plex Pro™ Human Cytokine Assay (Bio-Rad Laboratories, Hercules, CA, USA), following the manufacturer's protocol. This multiplex bead-based assay utilizes magnetic beads coated with specific anti-cytokine antibodies, enabling the simultaneous quantification of multiple cytokines within a single sample.

Prior to measurement, plasma samples were acid-activated to detect total TGF-β concentrations. For this purpose, 25 µL of each plasma sample was mixed with 25 µL of freshly prepared 1N HCl and incubated for 10 min at room temperature. Neutralization was performed by adding 25 µL of 1.2N NaOH/0.5M HEPES buffer to ensure optimal assay conditions. Magnetic beads coated with antibodies specific for TGF-β1, TGF-β2, and TGF-β3 were vortexed and diluted according to the manufacturer's instructions. A 50 µL aliquot of the bead mixture was added to each well of a 96-well plate. Subsequently, 50 µL of activated plasma samples, blank controls, and standards were added to the respective wells. The plate was sealed and incubated for 1 h at room temperature with gentle shaking (850 rpm). Following incubation, wells were washed three times with Bio-Plex Wash Buffer, and 25 µL of biotinylated detection antibody solution was added to each well. The plate was incubated for 30 min at room temperature with shaking. This was followed by the addition of 50 µL of streptavidin-phycoerythrin (PE) and an additional 10-min incubation. After three final wash cycles, beads were resuspended in 125 µL of assay buffer, and fluorescence intensity corresponding to cytokine concentrations was measured using the Bio-Plex 200 System with Bio-Plex Manager™ software (Bio-Rad). Fluorescence signals were analyzed using a standard curve generated from known cytokine concentrations. Data were statistically analyzed using STATISTICA 10.0 software. Due to the normal distribution of TGF-β concentration values, differences between groups were assessed using Student's *t*-test, with statistical significance set at $p < 0.05$. This methodology ensured high sensitivity and specificity for TGF-β isoform quantification, allowing for the assessment of cytokine dynamics in patients with thyroid disorders and obesity.

The study was approved by the bioethics committee by resolution number PCN/CBN/0052/KB1/125/22 of 29 November 2022.

3. Results

In this study, we analyzed perioperative levels of TGF-β1, TGF-β2, and TGF-β3 in patients diagnosed with differentiated thyroid cancer (DTC) and compared them with levels observed in obese patients with benign thyroid disease, specifically neutral nodular goiter. The results reveal several significant differences in cytokine expression patterns based on both disease type and patient body mass index (BMI).

Among patients with DTC, there was a statistically significant postoperative increase in all three isoforms of transforming growth factor beta. The concentration of TGF-β1 rose to 210,000 pg/mL, TGF-β2 increased to 360 pg/mL, and TGF-β3 reached 170 pg/mL following surgical removal of malignant thyroid tissue. These elevations were significantly higher compared to levels observed in the obese benign goiter group ($p < 0.05$ for all isoforms), suggesting an association between malignancy and heightened TGF-β signaling. This increase may reflect the systemic immunological and inflammatory changes associated with tumor biology and surgical response.

In contrast, within the obese nodular goiter group, body weight did not appear to affect preoperative levels of any TGF-β isoform. Pre-surgical measurements of TGF-β1, TGF-β2, and TGF-β3 did not vary significantly across different BMI categories in this non-malignant cohort ($p > 0.05$). This finding suggests that, in the absence of malignancy, obesity alone does not substantially alter baseline circulating levels of these cytokines, at least in the context of benign thyroid disease.

However, when evaluating the impact of obesity in the postoperative period, notable differences emerged. Obese patients demonstrated significantly lower postoperative TGF-β1 and TGF-β2 levels compared to their normal-weight counterparts. Specifically, TGF-β1 levels in obese patients were reduced to 100,000 pg/mL and TGF-β2 to 30 pg/mL. This contrast was statistically significant, with a p-value of 0.03. These findings suggest a potential inverse relationship between adiposity and postoperative cytokine levels for certain isoforms. One possible explanation may be the altered immune function or cytokine signaling pathways in obese individuals, which could attenuate the systemic inflammatory response following surgery.

Interestingly, this trend was not observed for TGF-β3. Postoperative levels of this isoform did not differ significantly between obese and non-obese patients ($p > 0.05$), indicating that TGF-β3 expression might be less sensitive to metabolic or weight-related factors in the postoperative setting. This observation also underscores the isoform-specific regulation of TGF-β cytokines and suggests a unique biological role for TGF-β3 that warrants further exploration.

To summarize the numerical data and statistical findings:

- **Differentiated Thyroid Cancer (postoperative):**
  - TGF-β1: 210,000 pg/mL
  - TGF-β2: 360 pg/mL
  - TGF-β3: 170 pg/mL
  - Statistically significant vs. benign goiter group ($p < 0.05$)
- **Obese patients with benign goiter (preoperative):**
  - TGF-β1, β2, β3: No significant variation with BMI ($p > 0.05$)
- **Obese patients (postoperative):**
  - TGF-β1: 100,000 pg/mL
  - TGF-β2: 30 pg/mL
  - Significantly lower vs. normal-weight patients ($p = 0.03$)
  - TGF-β3: No significant difference vs. normal-weight patients ($p > 0.05$)
- **Normal-weight patients (postoperative):**
  - TGF-β1 and TGF-β2 levels higher than in obese group
  - TGF-β3: no notable difference observed

Taken together, these results suggest a multidimensional relationship between thyroid pathology, metabolic status, and immune signaling. While cancer itself appears to drive elevated TGF-β activity postoperatively, obesity may have a dampening effect—at least on TGF-β1 and TGF-β2—potentially due to chronic immune adaptation or altered cytokine clearance mechanisms. The lack of significant difference in TGF-β3 levels postoperatively between obese and non-obese patients may reflect a more complex or tissue-specific regulatory mechanism that is not solely dependent on systemic inflammatory status or metabolic health.

These findings, presented in Table 1, support the hypothesis that TGF-β isoforms may serve not only as biomarkers of malignancy and surgical response but also as potential indicators of the interaction between metabolic status and thyroid disease. Future studies

with more detailed stratification (e.g., by tumor histology or nodal status) will be needed to clarify these relationships further.

Table 1. Observed levels of TGF β1, TGF β2, and TGF β3 in different patient groups, along with the corresponding statistical significance.

Group	TGF β1 (pg/mL)	TGF β2 (pg/mL)	TGF β3 (pg/mL)	Statistical Significance
Differentiated Thyroid Cancer (post-op)	210	360	170	$p < 0.05$
Obese Patients with Neutral Nodular Goiter	Pre-op: Not affected by BMI ($p > 0.05$)	Not affected by BMI ($p > 0.05$)	Not affected by BMI ($p > 0.05$)	N/A
Obese Patients (post-op)	100	30	N/A	$p = 0.03$ for TGF β1 and β2
Normal-Weight Patients (post-op)	Higher than obese patients	Higher than obese patients	N/A	N/A
TGF β3 (post-op, obese vs. normal weight)	N/A	N/A	No significant difference	$p > 0.05$

4. Discussion

Our findings suggest a significant correlation between obesity and increased TGF-β levels in patients with thyroid disorders. The observed elevation in TGF-β1, TGF-β2, and TGF-β3 levels among obese individuals with nodular goiter highlights the potential role of TGF-β as a link between metabolic dysfunction and thyroid disease. These results align with previous studies demonstrating the involvement of chronic inflammation and adipokine dysregulation in obesity-related thyroid pathophysiology [9].

TGF-β has a well-documented role in tumorigenesis, particularly in thyroid cancer progression. In the early stages of cancer, TGF-β functions as a tumor suppressor by inhibiting cellular proliferation and inducing apoptosis. However, as the disease progresses, cancer cells develop mechanisms to evade TGF-β-mediated growth suppression, allowing this cytokine to promote epithelial-to-mesenchymal transition (EMT), immune evasion, and metastasis [10]. This dual role of TGF-β may explain the elevated levels observed in patients with DTC, particularly those with more aggressive tumor phenotypes.

Furthermore, obesity has been linked to a state of chronic low-grade inflammation, characterized by elevated levels of pro-inflammatory cytokines and adipokines such as leptin, resistin, and tumor necrosis factor-alpha (TNF-α) [11]. These factors contribute to insulin resistance and metabolic dysfunction, which in turn may influence thyroid cancer progression [12]. Our study supports this hypothesis, as higher TGF-β levels were noted in obese patients, suggesting a potential interaction between metabolic inflammation and thyroid malignancy.

Interestingly, TGF-β is also involved in adipose tissue homeostasis. In obesity, chronic inflammation and dysregulated adipokine signaling create a microenvironment conducive to fibrosis and metabolic dysfunction [2,13]. TGF-β contributes to adipose tissue fibrosis by stimulating extracellular matrix deposition, thereby reducing adipocyte plasticity and impairing metabolic homeostasis [6]. This fibrotic response further exacerbates insulin resistance and systemic inflammation, potentially fueling thyroid cancer progression [7].

Another key observation in our study was the impact of surgical intervention on TGF-β levels. We noted a significant post-surgical decline in circulating TGF-β levels, particularly in patients with nodular goiter. This finding suggests that removal of affected thyroid tissue may help alleviate systemic inflammation, leading to an overall reduction in cytokine dysregulation. In DTC patients, the decline in TGF-β levels post-surgery could indicate a reduced tumor burden and diminished tumor-promoting signaling. However, it

remains unclear whether these reductions are sustained over time, highlighting the need for long-term follow-up studies.

The clinical implications of our findings are substantial. Given the role of TGF-β in both obesity and thyroid cancer, targeted therapies aimed at modulating TGF-β signaling may offer new treatment avenues. TGF-β inhibitors have been explored in oncology, particularly for advanced and metastatic cancers [3]. However, the challenge lies in selectively targeting the pro-tumorigenic effects of TGF-β while preserving its physiological functions [12]. Future therapeutic strategies should focus on personalized approaches that consider the patient's metabolic status and TGF-β expression profiles [13].

Beyond pharmacological interventions, lifestyle modifications may also play a crucial role in managing obesity-associated thyroid disease [14]. Weight loss has been shown to reduce chronic inflammation, improve insulin sensitivity, and lower adipokine secretion [15]. These metabolic improvements may, in turn, reduce TGF-β signaling activity, potentially lowering the risk of thyroid malignancy or improving prognosis in affected individuals [16]. Dietary interventions rich in anti-inflammatory nutrients, such as omega-3 fatty acids and polyphenols, could further modulate TGF-β activity and improve metabolic health [17].

While the focus of our study was on perioperative variations in TGF-β isoforms, we recognize that several clinical and pathological variables—such as histological subtype of thyroid cancer, tumor staging, lymph node involvement, gland volume in goitrous cases, and ATA risk classification—may act as important confounders that were not directly analyzed. These factors can significantly influence both local and systemic cytokine expression and should be considered when interpreting our findings. For instance, aggressive histological variants (e.g., tall-cell or diffuse sclerosing subtypes) may inherently produce different cytokine profiles than classic papillary carcinoma. Similarly, more advanced tumor stages or extensive lymph node metastases might amplify the immune response and affect circulating TGF-β levels. Gland volume in nodular goiter could influence tissue hypoxia, vascularity, and mechanical stress, all of which may modulate cytokine release. Though these parameters were outside the scope of our current analysis, we acknowledge their potential relevance and recommend that future studies incorporate these variables to enhance the robustness and generalizability of findings.

Despite these promising findings, larger, multi-center studies are required to confirm these observations and provide more robust data on the long-term impact of TGF-β modulation in thyroid disease and obesity. Additionally, mechanistic studies exploring the precise pathways through which obesity-driven inflammation influences TGF-β signaling in thyroid tissue are warranted. Understanding the interplay between metabolic dysfunction, cytokine signaling, and thyroid carcinogenesis will be crucial for developing more effective therapeutic strategies.

In conclusion, our study highlights the interplay between obesity, TGF-β signaling, and thyroid cancer. The findings underscore the importance of metabolic health in thyroid disease progression and suggest potential therapeutic targets for intervention. Future research should focus on refining TGF-β-targeted strategies while accounting for individual clinical characteristics and underlying disease complexity.

5. Conclusions

This study highlights significant postoperative alterations in TGF-β1, -2, and -3 levels in differentiated thyroid cancer (DTC) patients compared to obese individuals with nodular goiter. The findings suggest that TGF-β plays a critical role in tumor microenvironment remodeling following surgery, with potential implications for residual tumor cell signaling and overall disease progression.

Key observations include the following:

- A postoperative rise in TGF-β levels in DTC patients, indicating a response to surgical stress and potential involvement in cancer progression. This aligns with previous findings that TGF-β1 acts as a tumor suppressor in early-stage cancers but promotes tumor progression and metastasis in later stages.
- A lack of preoperative differences in TGF-β levels in obese patients with nodular goiter, suggesting that obesity alone does not inherently elevate TGF-β concentrations in thyroid pathology. This finding challenges previous assumptions that obesity-driven inflammation universally increases TGF-β activity in all tissue types.
- A distinct postoperative reduction in TGF-β1 and TGF-β2 levels in obese patients compared to normal-weight individuals, pointing to a metabolic rather than purely inflammatory response. This observation suggests that chronic low-grade inflammation associated with obesity may alter cytokine regulation in a manner distinct from malignancy-driven pathways.

Despite the influence of surgical trauma on cytokine levels, several factors suggest that the observed changes are not solely iatrogenic. The differential postoperative TGF-β responses between DTC and obese nodular goiter patients imply that underlying pathology plays a more significant role than the surgical act itself. Additionally, the specific reduction of TGF-β1 and TGF-β2 in obese patients, rather than a uniform increase across all groups, suggests a metabolic mechanism rather than a generalized inflammatory response. If these changes were purely a result of surgical trauma, a more homogeneous pattern of TGF-β alterations across all patient groups would be expected, which was not observed in this study.

These findings underscore the complex interplay between thyroid cancer, obesity, and TGF-β signaling. Understanding these mechanisms is essential for developing more effective therapeutic strategies tailored to patient-specific metabolic and oncologic profiles. The observed differences in cytokine dynamics highlight the need for further research into the molecular pathways that govern TGF-β regulation in both malignant and metabolic thyroid disorders. Future studies should aim to elucidate the precise role of TGF-β isoforms in these conditions, potentially paving the way for targeted interventions that could improve clinical outcomes for both DTC patients and individuals with obesity-related thyroid pathology.

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Informed Consent Statement: Not applicable.

Data Availability Statement: The data supporting results can be found in Chair and Clinical Department of General and Endocrine Surgery, Faculty of Health Sciences, Medical University of Silesia in Katowice, Poland.

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