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**Case Report**

# Correlation Between Glycemic Control and Serum Thyroglobulin Levels in a Patient With RAI-Refractory Thyroid Cancer

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## Abstract

Diabetes is a risk factor for thyroid cancer development. Serum thyroglobulin (Tg) levels are useful as sensitive and specific tumor markers for monitoring radioiodine (RAI)-refractory thyroid cancer; however, the impact of glycemic control on serum Tg levels is poorly understood. Here, we present a case of a female patient with lung metastases of RAI-refractory thyroid cancer in whom glycemic control may have influenced the serum Tg levels. Despite receiving thyroid-stimulating hormone suppression therapy, her serum Tg levels remained elevated. Subsequently, she developed type 2 diabetes and was administered antidiabetic medications for 6 years. Throughout the course of diabetes management, her serum Tg levels fluctuated according to the level of glycemic control, showing a strong correlation with her hemoglobin A1c levels ($r = 0.92$, $P < .01$). Similar to the serum levels of other tumor markers, such as the carcinoembryonic antigen and carbohydrate antigen 19-9, the serum levels of Tg can be influenced by glycemic control. Therefore, serum Tg levels in patients with RAI-refractory thyroid cancer and diabetes should be monitored with attention to glycemic control.

**Key Words:** radioiodine-refractory thyroid cancer, thyroglobulin, type 2 diabetes, glycemic control, metformin

## Introduction

Differentiated thyroid cancer generally has a favorable prognosis when treated with surgical resection and radioiodine (RAI) therapy; however, refractoriness to RAI therapy is associated with a poor prognosis (1). Nevertheless, the progression in most cases of RAI-refractory thyroid cancer is slow, and conservative intervention with thyroid-stimulating hormone (TSH) suppression therapy is recommended for patients with stable persistent disease. In this situation, serum thyroglobulin (Tg) levels are used as sensitive and specific tumor markers for the monitoring of cancer progression (1).

Diabetes is a known risk factor for thyroid cancer (2). Despite numerous reports that have demonstrated an association between the 2 conditions, no study has explored the impact of glycemic control on serum Tg levels after RAI therapy. Here we present a case of a female patient with RAI-refractory thyroid cancer and diabetes in whom glycemic control may have influenced the serum Tg levels. This case indicates that the serum Tg levels in patients with RAI-refractory thyroid cancer and diabetes should be monitored with attention to glycemic control.

## Case Presentation

The patient (aged 25 years at the time) presented to our hospital in March 2003, following the detection of diffuse granular opacities via plain chest radiography. Palpation revealed a thyroid nodule, and thyroid ultrasonography and cytology findings suggested papillary thyroid carcinoma. The patient was diagnosed with papillary thyroid carcinoma with lung metastasis and underwent total thyroidectomy and neck lymph node dissection in April 2003. Pathological examination confirmed the presence of papillary thyroid carcinoma (pT4aN1b).

In May 2003, the patient underwent RAI therapy. Posttreatment scintigraphy revealed diffuse isotope accumulation in the lungs. The therapy was repeated because no effective treatments other than RAI therapy were available at the time (Fig. 1A).

In May 2013, scintigraphy revealed metastatic lesion accumulation in the lung after the 11th RAI therapy session (Fig. 1B). We concluded that the patient was refractory to RAI therapy because the serum Tg level under the TSH stimulation increased compared with the previous treatment levels; thus, treatment was discontinued. The patient then underwent TSH suppression therapy. Levothyroxine dosage was increased from 150 mcg/day to 200 mcg/day for complete TSH suppression; however, the serum Tg levels remained elevated (Fig. 2). Serum Tg levels were measured using the ECLusys Tg kit (Roche Diagnostics) until May 2015 and the ECLusys Tg II kit (Roche Diagnostics) from June 2015.

In May 2017, at 39 years of age, the patient was diagnosed with type 2 diabetes for the first time. With the exception of thyroid cancer, the patient's medical history was unremarkable.

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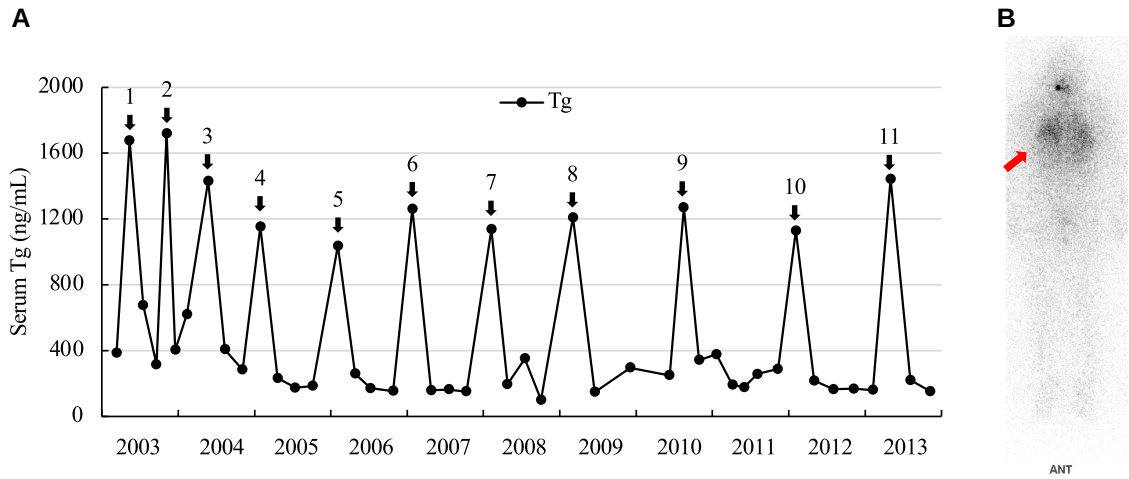


**Figure 1.** (A) Changes in the serum Tg levels of the patient across 11 sessions (cumulative dose, 1100 mCi) of RAI therapy after total thyroidectomy. Serum Tg levels at the arrows indicate TSH-stimulated levels under levothyroxine withdrawal. The serum Tg levels were measured using the ECLusys Tg kit (Roche Diagnostics). (B) A whole-body scan performed after the 11th RAI therapy session revealed a diffused lung uptake (arrow). Conversion factors used for the conversion of conventional units to SI units are Tg: 1.0 mcg/L = 1.0 ng/mL. Abbreviations: RAI, radioiodine; Tg, thyroglobulin; TSH, thyroid-stimulating hormone.

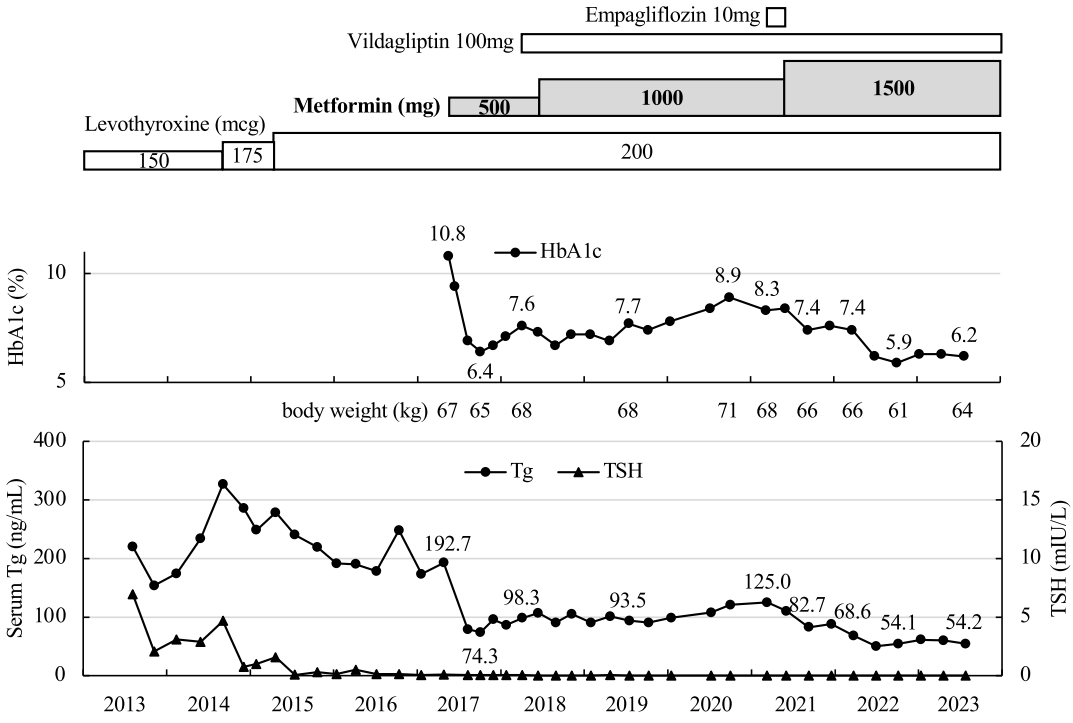


**Figure 2.** Changes in the serum Tg and HbA1c levels following radioiodine therapy completion. The patient developed type 2 diabetes in May 2017 and was started on metformin. The serum Tg levels were measured using the ECLusys Tg kit (Roche Diagnostics) until May 2015 and the ECLusys Tg II kit (Roche Diagnostics) from June 2015. The serum TSH levels were measured using the ECLusys TSH kit (Roche Diagnostics). Conversion factors used for the conversion of conventional units to SI units are Tg: 1.0 mcg/L = 1.0 ng/mL and HbA1c: 1.0 IFCC mmol/mol = 10.93 NGSP %—23.52 mmol/mol. Abbreviations: HbA1c, hemoglobin A1c; IFCC, International Federation of Clinical Chemistry and Laboratory Medicine; NGSP, National Glycohemoglobin Standardization Program; Tg, thyroglobulin; TSH, thyroid-stimulating hormone.

## Diagnostic Assessment

Laboratory findings included a hemoglobin A1c (HbA1c) level at 10.8% (94.5 mmol/mol) (reference range: 4.6-6.2%; 26.7-44.2 mmol/mol), fasting glucose level at 231 mg/dL (12.8 mmol/L) (reference range: 70-110 mg/dL; 3.9-6.1 mmol/L), and immunoreactive insulin level at 19.6 mcU/mL (135.6 pmol/L) (reference range: 5-15 mcU/mL; 34.6-103.8 pmol/L). Her renal function was normal with a serum

creatinine level of 0.54 mg/dL (47.7 mcmol/L) (reference range: 0.40-0.80 mg/dL; 35.4-70.7 mcmol/L). With a height, weight, and body mass index of 151 cm, 67.0 kg, and 29.7 kg/m$^2$, respectively, the patient was considered overweight.

## Treatment

Having been diagnosed with type 2 diabetes, the patient was suspected of having insulin resistance; treatment was initiated with oral metformin (500 mg/day) and diet modification (Fig. 2). Five months after metformin initiation, the HbA1c level improved to 6.4% (46.5 mmol/mol).

In April 2018, after the HbA1c level increased to 7.6% (59.6 mmol/mol), the patient was prescribed oral vildagliptin (100 mg/day), and the metformin dose was increased to 1000 mg/day. The HbA1c level remained stable at approximately 7.0% (53.0 mmol/mol) for some time; however, as the body weight increased, the HbA1c level increased to 8.9% (73.8 mmol/mol) in September 2020.

In March 2021, oral empagliflozin (10 mg/day) was added to the regimen but was discontinued 3 months later due to genital itching. Thereafter, the metformin dose was increased to 1500 mg/day. Following weight loss, the HbA1c levels improved and stabilized at approximately 6.0% (42.1 mmol/mol) in 2023.

## Outcome and Follow-up

The patient's serum Tg level at metformin initiation was 192.7 ng/mL (192.7 mcg/L), which decreased to 74.3 ng/mL (74.3 mcg/L) 5 months later (Fig. 2). Subsequently, the serum Tg level increased to 125.0 ng/mL (125.0 mcg/L), consistent with the worsening HbA1c levels. After the metformin dose was increased to 1500 mg/day, the serum Tg level decreased to 54.2 ng/mL (54.2 mcg/L), consistent with the improvement in the HbA1c level. Throughout the 6-year treatment course, the patient's serum TSH levels remained suppressed, and anti-Tg antibody levels, measured using the ECLusys Anti-Tg kit (Roche Diagnostics), were consistently ≤14 IU/mL (reference range: <28 IU/mL). Chest computed tomography was performed annually, and the size of the lung tumors did not change significantly between 2016 and 2022 (Fig. 3). No other obvious signs of recurrence were observed.

## Discussion

In this case, the serum Tg levels fluctuated similarly to the level of glycemic control, and a strong correlation ($r = 0.92$, $P < .01$) was observed between the HbA1c and serum Tg levels (Fig. 4). The manufacturer's literature for the ECLusys Tg kit did not mention any significant interference caused by hyperglycemia. This suggests that the serum Tg levels were influenced by glycemic control. In patients with diabetes who do not have any malignancy, the level of tumor markers, such as carcinoembryonic antigen and carbohydrate antigen 19-9 (known glycoproteins and carbohydrate chain antigens), is positively correlated with glycemic control (3, 4). The mechanism of the association between these tumor markers and glycemic control remains unclear; it presumably involves increased synthesis of glycoproteins and carbohydrate chain antigens associated with hyperglycemia or decreased catabolism due to glycation. Conversely, in patients with diabetes who have malignancy, few studies have demonstrated the relationship between tumor markers and glycemic control. Assessing the impact of glycemic control may be challenging due to both the low specificity of these tumor markers and changes in the clinical condition resulting from rapid disease progression and treatment interventions. Tg is a glycoprotein synthesized by thyroid follicular cells. The serum Tg after surgery and RAI therapy is considered to be derived from thyroid cancer cells, making it a highly sensitive and specific tumor marker (1). Similar to most RAI-refractory thyroid cancers, the cancer progression in our patient was slow, and additional therapeutic intervention was not required. This allowed us to conduct a long-term observation of serum Tg and HbA1c levels, which may reveal their association.

Our patient presented with diabetes and overweight. Diabetes and obesity are recognized as risk factors for the development of various cancers, including thyroid cancer (5, 6). The increase in cellular metabolic products (such as reactive oxygen species and advanced glycation end-products associated with hyperglycemia), as well as obesity-associated hyperinsulinemia, are known to induce cell growth, proliferation, and antiapoptotic effects (2, 7). In this study, we were not able to fully examine whether metabolic parameters other than HbA1c, such as insulin levels and body weight, influence serum Tg levels. Further investigation with a larger number of cases will help elucidate the mechanism of the association between serum Tg levels and glycemic control.

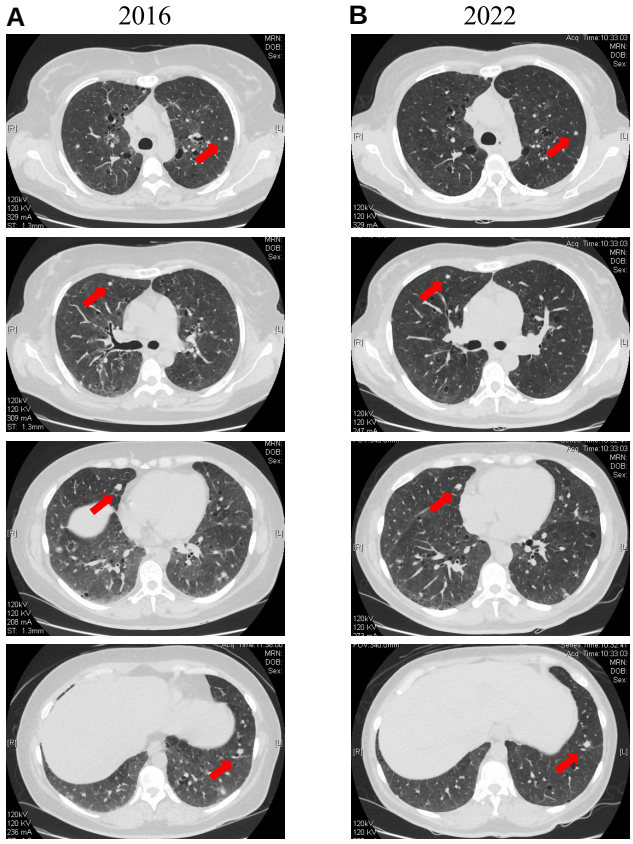


**Figure 3.** Comparison of chest CT scans. (A) Chest CT scan obtained in October 2016 before initiating metformin therapy. (B) Chest CT scan obtained in October 2022; that is, 5 years after starting metformin treatment. The size of the lung tumors (arrows) did not change significantly between 2016 and 2022. Abbreviations: CT, computed tomography.

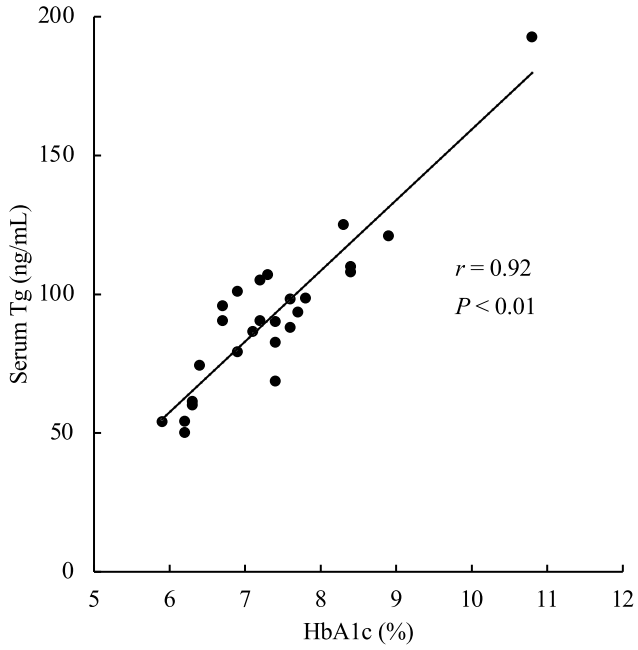


**Figure 4.** Correlation between serum Tg and HbA1c levels throughout the course of diabetes management. Conversion factors used for the conversion of conventional units to SI units are Tg: 1.0 mcg/L = 1.0 ng/mL and HbA1c: 1.0 IFCC mmol/mol = 10.93 NGSP %—23.52 mmol/mol. Abbreviations: HbA1c, hemoglobin A1c; IFCC, International Federation of Clinical Chemistry and Laboratory Medicine; NGSP, National Glycohemoglobin Standardization Program; Tg, thyroglobulin; TSH, thyroid-stimulating hormone.

Cancer cells undergo significant changes in their glucose metabolic programs and depend on glycolysis even under aerobic conditions (commonly called the Warburg effect), unlike normal cells, which typically produce adenosine triphosphate through oxidative phosphorylation (8). Therefore, cancer cells require a substantial amount of glucose, and targeting glucose metabolism is considered a rational strategy in cancer treatment. This case showed a significant decrease in serum Tg levels with improved glycemic control; however, no change was observed in the tumor size on computed tomography. Serum Tg levels generally correlate with tumor size during the natural history of thyroid cancer. However, it is well known that serum TSH levels affect serum Tg levels without changing the apparent tumor size. Although this case suggests that glycemic control may also influence serum Tg levels, further investigation is needed to determine whether the decrease in serum Tg levels with improved glycemic control impacts prognosis similarly to TSH suppression therapy.

A notable aspect in our case was the use of metformin. Aside from its blood glucose-lowering effects, metformin exerts various actions, including combating cancer (9). The indirect anticancer effects of metformin are exerted through the lowering of blood glucose levels and improvement of insulin sensitivity, whereas the direct anticancer effects are exerted mainly through the activation of adenosine monophosphate-activated protein kinase and inhibition of the mammalian target of rapamycin pathway, subsequently leading to inhibition of protein synthesis and cell proliferation (9). However, reports on the efficacy of metformin against the incidence and prognosis of thyroid cancer in humans have yielded conflicting results (10). The limitations of these studies, such as heterogeneous study designs, limited sample sizes, unassessed dose–response effects, and immortal time bias, should be considered. To elucidate the anticancer effects of metformin, well-designed prospective studies with larger sample sizes are needed.

In conclusion, glycemic control may influence serum Tg levels; therefore, the serum Tg levels in patients with RAI-refractory thyroid cancer and diabetes should be monitored with attention to glycemic control. Further investigation is needed to determine whether the decrease in the serum Tg levels with improved glycemic control has an impact on prognosis.

## Learning Points

- Serum Tg levels are useful as sensitive and specific tumor markers for monitoring RAI-refractory thyroid cancer.
- Glycemic control may influence serum Tg levels in patients with RAI-refractory thyroid cancer.
- Cancer cells undergo significant changes in their glucose metabolic programs; anticancer treatments that target glucose metabolism may be a rational strategy.

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## Contributors

All authors made individual contributions to authorship. Y.H. was involved in the diagnosis and management of this patient and manuscript submission. T.N., Y.F., K.F., T.I., and N.M. participated in the discussion of the results. All authors reviewed and approved the final draft.

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## Disclosures

None declared.

## Informed Patient Consent for Publication

Signed informed consent obtained directly from the patient.

## Data Availability Statement

Original data generated and analyzed during this study are included in this published article.

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