

Proenkephalin-A as a Biomarker for Type 2 Diabetes in Women with Thyroid Disorders

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Abstract

Background: The thyroid is a vital endocrine gland that regulates growth, metabolism, and development. Thyroid dysfunction (TD) and diabetes mellitus (DM) are two prevalent endocrine disorders with overlapping pathophysiological features.

Objective: To investigate the potential role of proenkephalin-A (PENK-A) as a diagnostic and predictive biomarker for type 2 diabetes in women with thyroid dysfunction.

Methods: A total of 130 women aged 25–55 years were enrolled in the study, including 100 patients with thyroid disorders and 30 healthy controls. The study was conducted from December 2024 to April 2025 at Al-Kindy Center for Endocrinology and Diabetes in Baghdad. Participants were categorized into four subgroups based on the presence or absence of hypothyroidism, hyperthyroidism, and DM. Serum levels of PENK-A, TSH, T3, T4, and HbA1c were measured using different principles of ELISA technique, while (FBG) Fasting Blood Glucose was determined by the enzymatic colorimetric method using a glucose kit from Randox. To express the data, the mean $\pm$ SD was used.

Results: PENK-A levels were significantly elevated in patients with both thyroid dysfunction and type 2 diabetes compared to non-diabetic patients and controls. PENK-A demonstrated high diagnostic performance in distinguishing hypothyroidism and hyperthyroidism patients with DM from those without DM, achieving an outstanding AUC of 0.942 and 0.813, respectively.

Conclusions: Proenkephalin-A may serve as a sensitive and specific biomarker for predicting and monitoring type 2 diabetes in patients with thyroid disorders.

Key words: Diabetes Mellitus; Hyperthyroidism; Hypothyroidism; Proenkephalin-A; Thyroid disorder.

Received: June 2025
Revised: Sept. 2025
Accepted: Sept. 2025
Published Online: Sept. 2025
Published: Oct. 2025

Introduction

The thyroid gland is a bilobed, butterfly-like organ situated anterior to the trachea below the larynx. The functional component, the follicle of the thyroid, is a sac-like structure made up of one layer of cuboidal thyrocytes surrounding the follicle that produces colloid, a large iodine-free, tyrosine-containing glycoprotein, thyroglobulin (1,2). According to the American Thyroid Association, women are 5-8 times more likely than men to develop thyroid problems, with thyroid disorders affecting as many as one in eight women in their lifetime. Abnormalities of the thyroid affect many metabolic processes in the body and can possess a very substantial impact on overall health, life quality and reproductive processes (3). Hypothyroidism is caused by decreased thyroid hormone levels, triiodothyronine (T3), and thyroxine (T4) for any reason. Iodine insufficiency is the primary reason for hypothyroidism. Primary hypothyroidism occurs when thyroid gland function is decreased or absent, while overt hyperthyroidism, defined by high T4 and T3 with suppressed thyroid-stimulating hormone (TSH), occurs in 0.5%–2% of women at a rate four to five times

greater than men (4,5). Diabetes mellitus (DM) and thyroid dysfunction are closely related endocrine illnesses because they can make each other worse. Patients with diabetes are far more likely than individuals without the disease to have thyroid problems (6). The pathologies of DM and thyroid dysfunction (TD), two of the most common endocrine illnesses, overlap (7). DM has been associated with hypothyroidism (8). TD and DM are closely linked. Thyroid diseases affect the secretion, action, and metabolism of insulin so induce insulin resistance and lead to DM (9). Together, insulin, implicated in DM, and thyroid hormones engage in an intricate dance and serve to regulate the body's metabolism. In addition to the pancreas, the thyroid gland affects the body's metabolism. Hormones secreted by the thyroid gland regulate carbohydrate metabolism and insulin secretion (10). High blood glucose levels are a hallmark of diabetes mellitus, a chronic metabolic illness, primarily as a result of insulin resistance (11). The control of glucose homeostasis is also significantly influenced by thyroid hormones. Thyroid hormones may affect insulin secretion, among other ways, to change blood glucose levels. On the one hand, diabetes affects the thyroid gland function and performance, whereas thyroid hormones control pancreas and carbohydrate metabolism (12). Thyroid conditions and obesity frequently interact and their

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incidence has been rising for a number of years. Although hypothyroidism may be a contributing factor to increased body fat, there is a reciprocal association between thyroid function hormones and body mass index (BMI). The function of the thyroid can be improved by reducing adipose tissue, according to published research (13). The key to controlling type 2 diabetes is managing and preventing obesity. Weight loss can help avoid, manage and in some cases, remit DM (14).

The family of endogenous opioid polypeptide hormones known as enkephalins includes human proenkephalin (PENK). Mostly attaching in order to activate δ (delta)-opioid receptors, these hormones are generated in many organs (15). PENK, also known as preproenkephalin A, a precursor peptide, is broken down, and a 41 amino acid peptide known as proenkephalin A 119–159 is created as a byproduct fragment. The two main functionally mature forms of enkephalins, both methionine-enkephalin (Met-Enk) and leucine-enkephalin (Leu-Enk) are produced when this precursor molecule is cleaved, in addition to PENK (16). These enkephalin peptides have the ability to activate opioid receptors, which can affect physiological processes like stress reactions and pain perception (17). The presence of enkephalins in the central and peripheral nervous systems, as well as in the pancreas, liver, adipose, skeletal muscle, lungs, and heart, suggests that enkephalins participate in several biological processes, encompassing feeding behavior (18). Pancreatic islet cells additionally generate proenkephalins, which block the absorption of glucose and hence decrease the insulin response. Moreover, several additional physiological impacts have been documented, such as its impact on blood pressure and heart rate (19).

The present study aimed to determine the proenkephalin-A in women with thyroid disorders, with and without diabetes mellitus, and the possibility of considering Proenkephalin-A as a diagnostic and predictive biomarker for diabetes in these patients.

The high prevalence of thyroid disorders in the community and their related complications, like diabetes mellitus, is the main reason that led to the selection of this study topic.

Subjects and Methods

Research design and patients' selection

Research design: This is an analytical case-control study conducted at The Specialized Diabetes and Endocrinology Center in Baghdad from December 2024 until April 2025. The current study included 130 women with an age range of 25-55 years; 100 were female patients with thyroid dysfunction and 30 individuals as controls. The patients were allocated to four groups: G1: 25 non-diabetic women with hypothyroidism, G2: 25 diabetic women with hypothyroidism, G3: 25 non-diabetic women with

hyperthyroidism, and G4: 25 diabetic women with hyperthyroidism. Thirty healthy women were selected to act as the study controls.

Sample collection: Five ml of venous blood was obtained from patients and healthy volunteers. The serum was separated by centrifugation for 10 minutes. The serum was used for laboratory assessments, which included TSH, T3, T4, Proenkephalin-A, and fasting blood glucose (FBG). Thyroid hormones (T3 and T4) were determined by Competitive-ELISA detection method, while TSH hormone was determined by ELISA kit using the Sandwich-ELISA principle. Proenkephalin-A was estimated by ELISA kit based on sandwich ELISA technology. Fasting serum glucose was determined by the enzymatic colorimetric method using a glucose kit from Randox (20). While estimation of glycated hemoglobin (HbA1c) was assayed by the Elisa kit from MyBioSource, which employs the direct competitive inhibition enzyme immunoassay technique for the quantitative determination of human glycated hemoglobin A1c (GHbA1c) concentrations in lysate for RBC. The individuals' height, weight, and age were recorded. Body mass index (BMI) was calculated founded on the following equation: weight (kg) divided by the square of height (m^2) (21).

Exclusion criteria: Males, and all female patients with other autoimmune diseases, haematological diseases, pregnant women and thyroid tumors.

Ethical approval: The Helsinki Declaration's ethics were followed when collecting samples and data. In order to be included in the study, participants had to give their consent. Additionally, the Diabetes and Endocrinology Specialized Center ethics committee approved the research. The ethical approval was issued by the Ministry of Health to the Specialized Center for Endocrine and Diabetes Diseases at Al-Kindi Hospital, with reference number 126249, dated 18-12-2024.

Statistical analysis: To express the data, the mean $\pm$ standard deviation (SD) was used to investigate the differences between the patient and control groups using the student t-test. The Pearson correlation coefficient was employed to test correlations between variables. The p value of ≤ 0.05 was considered statistically significant. The receiver operating characteristics (ROC) curve was employed to evaluate the performance of diagnostic tests.

Results

The mean $\pm$ SD levels of TSH, T3, T4, BMI, FBG, HbA1c, and PENK in controls (C), non-DM women with hypothyroidism (G1), DM women with hypothyroidism (G2), non-DM women with hyperthyroidism (G3), and DM women with hyperthyroidism (G4) groups were shown in **Table 1**. In comparison to the controls, TSH levels in G1 and G2 were significantly higher ($P \leq 0.05$), but TSH levels in G3 and G4 were significantly lower. Additionally,

in comparison to the controls, the T3 and T4 levels in G1 and G2, as well as G3 and G4, respectively, were significantly lower ($P \leq 0.05$). FBG and HbA1c mean levels in both G2 and G4 were significantly higher than those in G1, G3, and controls.

The mean level of BMI was significantly higher ($P \leq 0.05$) in G1, G2, and G3, but not significantly so in G4, when compared to the controls. FBG and HbA1c

were significantly higher ($P \leq 0.05$) in G2 and G4 compared to controls, with a significant difference in mean FBG and HbA1c levels between G1 and G2, and between G3 and G4 respectively. The mean PENK levels were significantly higher ($P \leq 0.05$) in G2 and G4 compared to healthy controls, and significantly higher in G2 compared to G1, between G4 and G3.

Table 1: Mean±SD levels of the study parameters in the four study groups and controls

Parameters	Control No = 30	G1 No = 25	G2 No = 25	G3 No = 25	G4 No = 25
TSH (μ IU/mL)	2.2±0.89	6.0±1.64*	6.1±2.73*	0.04±0.01*	<i>b</i> * 0.8±0.64*
T3 (nmol/L)	1.2±0.02	0.8±0.21*	<i>a</i> * 1.0±0.39*	2.8±0.79*	3.3±0.81*
T4 (nmol/L)	80.2±6.35	71.8±10.13*	74.5±9.35*	100.2±17.08*	93.7±11.67*
BMI (Kg/m ²)	27.2±3.13	30.8±4.89*	33.6±5.70*	25.1±3.01*	27.0±3.63
FBG (mg/dl)	86.9±8.05	90.1±5.93	<i>a</i> * 186.2±17.17 *	88.8±6.26	<i>b</i> * 182.2±15.72*
HbA1c%	5.0±0.30	5.9±0.24*	7.8±0.80*	5.5±0.60*	<i>b</i> * 7.9±0.90*
PENK (pg/ml)	814.9±379.65	734.1±80.03*	<i>a</i> * 1534.4±257.26*	701.7±82.40	<i>b</i> * 1244.6±277.03*

* P -value < 0.05: significant; *t-test between all patients' groups and controls;

^a*t-test between G1 and G2; ^b* t-test between G3 and G4

The correlation coefficient (r) was calculated and tested between serum PENK and the other parameters (TSH, T3, T4, BMI, FBG, and HbA1c) and the four study groups and the Controls, the results of which are shown in **Table 2**. There were significant ($P \leq 0.05$) positive correlations between serum PENK with TSH, T3, T4, and BMI, and a significant negative correlation between PENK with FBG and HbA1c in the controls. Significant ($P \leq 0.05$) positive correlations were found between serum PENK with TSH and FBG, and significant negative correlations between PENK with T3, T4, BMI, and HbA1c in G1.

Significant negative correlations were found between PENK with TSH and HbA1c, and positive correlations between serum PENK with T3, T4, BMI, and FBG in G2. In non-DM patients with hyperthyroidism (G3), there were significant ($P \leq 0.05$) negative correlations between PENK and TSH, T3, T4, BMI, and significant positive correlations between serum PENK and FBG and HbA1C. Significant negative correlations were found between PENK and TSH and BMI, and significant ($P \leq 0.05$) positive correlations between serum PENK with T3, T4, FBG, and HbA1c in G4.

Table 2: Pearson correlation coefficient (r) and P-value between PENK and all studied parameters in controls and the four study groups

Parameters	Control	G1	G2	G3	G4
	r	r	R	r	r
TSH (μ IU/mL)	0.30*	0.28*	- 0.27*	- 0.15*	- 0.11*
T3 (nmol/L)	0.34*	- 0.05*	0.43*	- 0.30*	0.08*
T4 (nmol/L)	0.25*	- 0.05*	0.24*	- 0.43*	0.21*
BMI (kg/m ²)	0.17*	-0.16*	0.16*	-0.07*	-0.13*
FBG (mg/dl)	- 0.12*	0.28*	0.36*	0.01*	0.05*
HbA1c%	- 0.27*	- 0.10*	- 0.25*	0.09*	0.01*

* P -value <0.05: significant; *t-test between PENK and study parameters in patients and control groups

G1, G2, G3, and G4, the ROC test for the PENK marker showed a perfect cutoff value with 100% sensitivity and 80% specificity for G2, and a good cutoff value with 90% sensitivity and 75% specificity for G4, compared to the control groups. The Area under curve (AUC) of PENK for G2 and G4 were

0.942 and 0.813, which are higher than in G1 and G3 (0.573 and 0.560). These results suggest that PENK may be a good sensitive and specific biomarker for DM in thyroid patients better than in thyroid patients without DM. **Table 3** and **Figures 1, 2, 3** and **4** show the ROC test for PENK in the four study groups.

Table 3: Curve of Receiver Operating Characteristic (ROC) PENK between all patients' groups and control groups

Roc of PENK	Sensitivity	Specificity	Area under curve	Accuracy	Asymptotic Sig.	Cut off value
G1	100%	50%	0.573	0.90	0.106	616.291
G2	100%	80%	0.942	0.96	0.0416	1205.235
G3	85%	55%	0.560	0.79	0.104	643.934
G4	90%	75%	0.813	0.73	0.0725	960.892

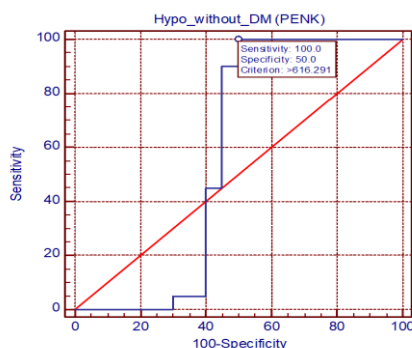


Figure 1: The ROC curve for PENK in hypothyroidism patients without DM and control

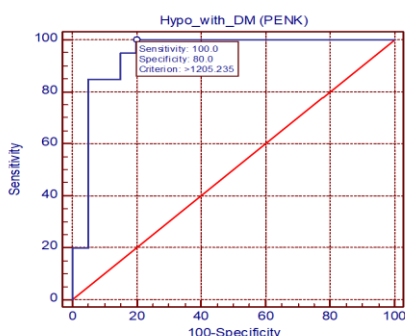


Figure 2: The ROC curve for PENK in hypothyroidism patients with DM and control

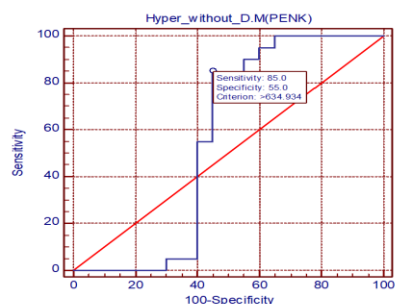


Figure 3: The ROC curve for PENK in hyperthyroidism patients without DM and control

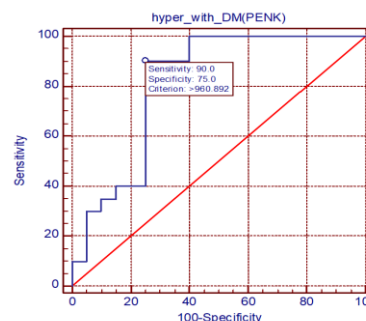


Figure 4: The ROC curve for PENK in hyperthyroidism patients with DM and controls

Discussion

This study was conducted on women with thyroid disorders under drug treatment, and over different disease durations. Glycated hemoglobin benefits as a diagnostic marker of blood glucose levels within the preceding three-month period (22). In the current study, PENK was tested for its potential as a diagnostic marker for diabetes in addition to the established routine diagnostic markers. The thyroid hormone has an essential function in controlling the metabolism of glucose. Both hypothyroidism and hyperthyroidism are associated with inadequate glycemic control because they both raise insulin resistance. Diabetes can alter how the TSH functions and how peripheral tissues convert T3 to T4, which can lead to hyperinsulinemia and insulin resistance. These lead to an increase in thyroid tissue proliferation, which causes goiter (23). Due to their agonistic and antagonistic effects on the actions of insulin in numerous organs, thyroid hormones play an essential part of preserving glucose homeostasis. Defects in glucose metabolism would result from any change in thyroid hormone levels. Hypothyroidism, for instance, deactivates the gluconeogenesis pathway, which lowers blood glucose levels (24). Pancreatic β -cell activity is impacted by low thyroid hormone levels in hypothyroidism, which prevents the stomach from absorbing glucose. Additionally, they impair skeletal muscle gluconeogenesis and peripheral glucose uptake due to increased insulin resistance and lower insulin sensitivity. Insulin resistance and hepatic glucose suspension result from hyperthyroidism's disruption of the insulin signaling system (25). While hypothyroidism may conceal clinical symptoms and

indicators of diabetes mellitus, hyperthyroidism alters insulin secretion, function, and clearance, which may result in hyperglycemia (26). Furthermore, compared to diabetic patients without TD, those with hypothyroidism may need varying dosages of insulin (27). Body weight increases with clinical hypothyroidism and decreases with hyperthyroidism. Nonetheless, there are differences in thyroid function among people whose thyroid hormone levels fall within the reference (physiologic) range (28). Although BMI was inversely correlated with TSH and favorably correlated with FT3 levels in men. For women, the relationship between BMI and TT3 and TT4 was statistically significant (29). The mechanism of thermogenesis may account for the causal association between differences in thyroid function and BMI. Through an increase in cellular activity to create ATP, thyroid hormones promote thermogenesis (30, 31). Additionally, the study's findings align with Ashgan Slman *et al.*, who reported higher TSH levels and lower T3 and T4 levels in hypothyroidism patients compared to controls (32). These results also agree with Eiman AA. Abass *et al.* (33) and Zeinab M. Al-Rubaei *et al.* (34). The results in the current study reveal a significant positive correlation between proenkephalin and FBS in thyroid disease groups. This finding agreed with Abed et al study, as indicators of glucose homeostasis, staniocalcin-1 and proenkephalin-A may be used in place of every additional conventional biomarker for predicting risk factors for diabetes mellitus (35). Enkephalins have been demonstrated to have a useful function in the metabolism of glucose. For instance, a low amount of enkephalin enhanced insulin secretion in vitro, and one of the earliest investigations, carried out in the 1980s, showed that the islets had opioid receptors (36). On the other hand, high in vitro enkephalin concentrations prevented insulin release, suggesting that enkephalins may control glucose homeostasis and insulin secretion (37). Opioid peptides are likely involved in modulating homeostatic signals received from the peripheral tissues, pharmacological studies have shown that opioid receptor agonists stimulate food intake, while opioid receptor antagonists suppress food intake (38). The opioid system is widely recognized for controlling energy balance and food intake. Enkephalins may also have a role in energy balance, along with the well-researched opioid receptors. By showing that when enkephalins are not present, glucose homeostasis is disturbed, possibly as a consequence of decreased insulin sensitivity, the study contributes to the body of existing research. Nonetheless, much more research is required to fully comprehend the function of enkephalins in this process. Additionally, we must ascertain how enkephalins interact with the neuropeptide systems that regulate glucose homeostasis and eating behavior. Examining enkephalin's central and peripheral actions

could help identify how they affect glucose homeostasis (39). Several factors which were not evaluated in this study, including social and cultural influences, diet, physical activity levels, assessment of energy expenditure and substrate preference, family history and compliance could have an impact on the outcomes.

Limitations:

This study has some limitations, including a small sample size, lack of representation of the entire population, and insufficient accurate patient data, especially regarding their lifestyle patterns. Limited funding and difficulty in recruiting enough participants were additional challenges. Therefore, future studies are needed to overcome these limitations and allow for broader generalization of the results.

Conclusion

The study concluded that proenkephalin-A (PENK-A) may serve as a diagnostic and predictive biomarker for type 2 diabetes in women with thyroid dysfunction. Moreover, the integration of PENK-A into clinical practice may provide additional value beyond conventional glycemic markers such as HbA1c, particularly in cases where standard markers are influenced by thyroid-related alterations or comorbidities. Identifying PENK-A as a novel biomarker may therefore enhance early detection, guide individualized treatment strategies, and improve long-term disease monitoring.

Authors' declaration

We confirm that all the Figures and Tables in the manuscript belong to the current study. Besides, the Figures and images, which do not belong to the current study, have been given permission for re-publication attached to the manuscript. The study was conducted in full accordance with local Good Clinical Practice guidelines and current legislation, and permission was obtained from our institutional ethics committee for the use of patient data for publication purposes. In addition to that participants' consent was taken for inclusion in the study.

Conflict of Interest: None

Funding: No specific grant from a public, private, or nonprofit funding organization was obtained for this study.

Data availability: Upon reasonable request, the corresponding author will make the data sets generated and/or analyzed during the current work available.

Authors' contributions:

Study conception & design: Eiman AA. Abass.
Literature search: Maryam A. Hassoun & Eiman AA. Abass.
Data acquisition & Data analysis: (Eiman AA. Abass).
Manuscript preparation Maryam A. Hassoun & Eiman AA. Abass,
editing & review: Eiman AA. Abass.

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How to Cite this Article?

Hassoun MA, Abass EA. Proenkephalin-A as a Biomarker for Type 2 Diabetes in Women with Thyroid Disorders with Thyroid Diseases. J Fac Med Baghdad [Internet]. Available

from: <https://iqjmc.uobaghdad.edu.iq/index.php/19JFacMedBaghdad36/article/view/3162>

البروانكيفالين A - كمؤشر حيوي لمرض السكري من النوع الثاني لدى النساء المصابات باضطرابات الغدة الدرقية

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الخلاصة

الخلفية: الغدة الدرقية هي غدة صماء حيوية تنظم النمو، الأيض، والتطور. اضطرابات الغدة الدرقية ومرض السكري هما من أكثر الاضطرابات الصماء شيوعاً ولهما خصائص فسيولوجية مرضية متداخلة.

الهدف: دراسة الدور المحتمل للبروانكيفالين- A (PENK-A) كمؤشر حيوي تشخيصي وتنبؤي لمرض السكري من النوع الثاني لدى النساء المصابات باضطرابات الغدة الدرقية.

المنهجية: شملت الدراسة 130 امرأة تتراوح أعمارهن بين 25-55 سنة، بما في ذلك 100 مريضة مصابة باضطرابات الغدة الدرقية و30 شخصاً سليماً كمجموعة تحكم. أجريت الدراسة من ديسمبر 2024 حتى أبريل 2025 في مركز الكندي للغدد الصماء والسكري في بغداد. تم تصنيف المشاركات إلى أربع مجموعات فرعية بناءً على وجود أو عدم وجود قصور الغدة الدرقية، فرط الغدة الدرقية، والسكري. تم قياس مستويات T3، TSH، PENK-A، T4، و HbA1c باستخدام تقنيات ELISA المختلفة، في حين تم تحديد سكر الدم الصائم بالطريقة اللونية الإنزيمية باستخدام عدة غلوكونز من Randox.

النتائج: كانت مستويات PENK-A مرتفعة بشكل معنوي ($P \leq 0.05$) لدى المريضات المصابات بكل من اضطرابات الغدة الدرقية ومرض السكري من النوع الثاني مقارنة بالمريضات غير المصابات بالسكري والمجموعة الضابطة. أظهر PENK-A أداءً تشخيصياً عالياً في التمييز بين مريضات قصور الغدة الدرقية وفرط الغدة الدرقية المصابات بالسكري ومن غير المصابات به، حيث بلغ AUC المتميز 0.942 و 0.813 على التوالي.

الاستنتاج: قد يكون البروانكيفالين- A مؤشراً حيوياً حساساً ومحددًا للتنبؤ ومتابعة مرض السكري من النوع الثاني لدى مريضات اضطرابات الغدة الدرقية.

الكلمات المفتاحية: البروانكيفالين- A، فرط الغدة الدرقية، قصور الغدة الدرقية، داء السكري، اضطراب الغدة الدرقية.