RESEARCH ARTICLE

A Comparative Study of Retinol-binding protein-4 and Progranulin in Iraqi Women with Thyroid Disorder

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ABSTRACT

Thyroid hormones (TH) regulate the metabolic processes required for normal development and growth; also, to organize metabolism in adults, any defect in thyroid function leads to abnormality in thyroid hormones level. The current study has been designed to find the relationship between retinol-binding protein-4 and progranulin in the serum of Iraqi women with hypothyroidism and hyperthyroidism, also, to study whether these patients are exposed to a risk of developing diabetes mellitus, and PGRN may be a biomarker in detection early stage of diabetes mellitus.

Materials and Methods: in this study, serum samples were obtained from 50 Iraqis women patients, [25 patients with hypothyroidism (G2) and 25 patients with hyperthyroidism (G3)] in addition to 25 healthy women as a control group (G1), their ages ranged from (30–55) years. The patients attended the Specialized Center for Endocrinology and Diabetes, Baghdad.

Results: the results in this study showed a highly significant decrease in RBP4 levels and a significant increase in PGRN levels in G2 and G3, respectively, compared with G1. Additionally, a considerable increase in BMI, FSG, and HbA1C levels in G2 and G3 Comparison with G1, and a significant difference between G2 and G3 patients.

Conclusions: The current study is the first to shed light on the relationship between PGRN and thyroid disorder, which provides a guide on the increase in PGRN levels of patients with a thyroid disorder, especially in patients with hyperthyroidism, related with metabolic and glucose abnormalities, and then, it may be a trustable predictive biomarker for detection early stage of diabetes mellitus type 2 in patients with a thyroid disorder. Also, there was a significant correlation between RBP4 and PGRN in these patients. In addition, these patients with hyperthyroidism were more likely to diabetes than patients with hypothyroidism.

Keywords: Diabetes mellitus, Hyperthyroidism, Hypothyroidism, Retinol binding protein-4, Progranulin.

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INTRODUCTION

There are fully certified effects for thyroid disorder on glucose homeostasis. Thyroid hormone activity in the liver, white adipose tissue, skeletal muscle, and pancreas affect plasma glucose concentration, insulin sensitivity, and carbohydrate metabolism. Decreased mitochondria activity has been a relation between a fine-described work of thyroid hormone and a disorder in type 2 diabetes (T2D).[1] Thyroid hormone (TH) controls metabolic operations required for average growth and development and organizes metabolism in adults.[2] Increased thyroid hormone is called hyperthyroidism, which supports a hypermetabolic state distinguished by an elevated resting energy consumption, weight loss, decreased cholesterol concentration, elevated lipolysis, and gluconeogenesis.[3] In contrast, hypothyroidism, which means a decrease in thyroid hormone levels, is linked with a hypometabolism state distinguished by decreased resting energy consumption, weight increase, raised cholesterol levels, and decreased in lipolysis plus gluconeogenesis.[4] Thyroxine (T4), 3,5,3'-triiodothyronine (T3), and reverse 3,5,3'-triiodothyronine (rT3) are the significant hormones generated via the thyroid gland, and they are regulated by thyroid-stimulating hormone (TSH) from the anterior pituitary gland.[5] Progranulin (PGRN) is a cytokine excreted by adipose tissue and is an excretory 593-amino acid glycoprotein with broad expression in various cells, like the immune system cells.[6] Also, PGRN is considered as a growth factor, similar to IGF-1, with inflammatory characteristics.[7] It is a cysteine-rich excreted protein with various pleiotropic functions and shares in many operations, like inflammation and tumorigenesis.[8] PGAN, as an adipokine, is associated with obesity and insulin resistance. The gene of PGRN is concentrated in the chromosome area of 17q21.32. In the Insulin Resistance Atherosclerosis Family Study, the tall arm

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of chromosome 17 was beforehand joined to visceral adipose tissue, waist circumference, and BMI in Hispanic members.[9] Furthermore, referring to a relationship with T2DM, the fasting glucose linkage signals were located with 17q in young European sib-pairs.[10]

Retinol-binding protein-4 (RBP4) is an excreted protein with approximately 21-kDa that transfers retinol (vitamin A) in the bloodstream. RBP4 was recognized as a significant adipokine that subscribes to insulin resistance in rodents and humans.[11] The human liver and adipose tissue essentially produce it. RBP4 is a plasma retinol carrier and deemed a new adipokine that acts as a significant job in insulin resistance.[12] In insulin-resistant rats and obese humans with diabetes, RBP4 concentrations are indicated to be elevated and could be regularized via insulin-sensitizing drugs.[13] Transthyretin (TTR) is a transport protein for thyroxine and retinol, binds with RBP4 forming a protein complex that blocks glomerular filtration and decreases RBP4 renal clearance.[14,15] By supporting its renal clearance, lowering TTR could decrease circulating levels of RBP4.[16] RBP4 is a protein that is synthesized essentially by hepatocytes and adipocytes. The irregular reproduction and migration of vascular smooth muscle cells, which is necessary for coronary atherosclerosis development, could be promoted by RBP4.[17] Furthermore, a high concentration of RBP4 promotes macrophage-derived foam cell generation through stimulating cholesterol uptake and hence accelerated atherosclerosis development.[18]

The endocrinopathies which are usually shown in routine practice, and they often coexist, are diabetes mellitus (DM) and thyroid dysfunction (TD). In both type 1 (T1DM) and type 2 (T2DM) diabetes mellitus patients, a great spread of thyroid disease is seen (19).[19] In type 2 diabetes mellitus (T2DM), both hypothyroidism and hyperthyroidism are more common.[20] Autoimmunity can describe the popular correlation between autoimmune thyroid diseases and T1DM; however, the relation between T2DM and TD is more complex.[21]

Aim of the Study

to find the association between retinol-binding protein-4 and progranulin in the serum of Iraqi women with hypothyroidism and hyperthyroidism, also, to study whether these patients are exposed to the risk of developing diabetes mellitus, and PGRN may be a biomarker in detection early stage of diabetes mellitus.

SUBJECTS AND METHODS

Subjects

Serum samples were obtained from 50 Iraqis women patients (25 patients with hypothyroidism (G2) and 25 patients with hyperthyroidism (G3)) in addition to (25) healthy women as a control group (G1), their ages ranged from 30-55 years, which enrolled in this study. The patients attended the Specialized Center for Endocrinology and Diabetes, Baghdad.

Methods

ELISA kits estimated retinol-binding protein -4 and progranulin from Elascience, No.E-EL-H1581, and E-EL-H1578, respectively. These kits were applied to the in vitro quantitative determination of human PGRN and RBP-4 concentrations in serum by uses the Sandwich-ELISA principle. Body mass index (BMI) was calculated founded on the following equation, weight (kg) divided by the square of height (m2).[22] Fasting serum glucose was determined by the enzymatic colorimetric method using a glucose kit from Randox.[23]

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. Thyroid hormones (T3, T4, and TSH) were determined by Electrochemiluminescence (ECL) on Roche Cobas e 411.

Statistical Analysis

Data were expressed as mean ± SEM. The multiple variations between patients and normal groups were tested by using a t-test, $p < 0.001$ and $p < 0.05$ that were reflected as highly significant and significant, respectively. Pearson's connection coefficient (r) is used for explaining the relationship between all studied parameters.

RESULTS

The results of the studied biochemical parameter in control (G1), hypothyroidism (G2), and hyperthyroidism (G3) patients are summarized in Table 1.

The results in this study showed a highly significant *($p < 0.001$)* and a significant *($p < 0.05$)* decrease in RBP4 levels in G2 and G3, respectively, when compared with G1, While there was no significant difference between G2 and G3. Besides, there was no significant *($p \geq 0.05$)* and a significant

Table 1: Levels (Mean ± SEM) of PGRN, RBP4, BMI, FSG, HbA1C, TT3, TT4, and TSH in G1, G2, and G3.

Groups parameters	*G1 No.(25)*	*G2 No.(25)*	*G3 No.(25)*
RBP4 (pg/ml)	42.4 ± 2.07	22.97 ± 3.90 *a***	27.12±4.71 *b** *c***
PGRN (pg/ml)	211.19 ± 11.82	265.25 ± 52.74 *a***	334.51±69.27 *b** *c***
BMI (Kg/m^2)	24.12±0.75	32.38 ± 0.92 *a***	30.06±0.92 *b*** *c**
FSG (mg/dl)	83.5 ± 1.69	95.1±1.84 a***	105.6±2.87 *b*** *c**
HbA1c %	4.91 ± 0.18	5.5 ±0.10 *a***	5.97±0.10 *b*** *c**
T T3 (nmol/L)	2.2 ± 0.23	0.95±0.14 *a***	5.61±0.14 *b*** *c***
T T4 (nmol/L)	104.41 ± 10.29	60.70±3.62 *a***	204.14±3.62 *b** *c***
TSH (µIU/ml)	2.72 ± 0.50	11.13±1.13 *a***	0.82±0.20 *b** *c***

** ($p < 0.05$), ** ($p < 0.001$), NS: Non-significant ($p \geq 0.05$).*
a: t-test between G1 and G2, b: t-test between G1 and G3, c: t-test between G2 and G3

($p < 0.05$) increase in PGRN levels in G2 and G3, respectively, compared with G1, also there was no significant elevation in PGRN level in G3 compared to G2.

Additionally, considerable increase *($p < 0.001$)* in BMI, FSG, and HbA1C levels in G2 and G3 Comparison with G1, and a significant difference *($p < 0.05$)* between G2 and G3 patients.

The current study shows a highly significant *($p < 0.001$)* decrease in TT3 and TT4 levels in G2, and a highly significant ($p < 0.001$) increase in TT3 and TT4 levels in G3 when compared with G1, also there were a highly significant ($p < 0.001$) differences in TT3 and TT4 levels between two patients groups (G2 and G3).

There was a highly significant increase ($p < 0.001$) in the TSH level in G2 and a significant *($p < 0.05$)* decrease in TSH level in G3 as paralleled to the G1. Moreover, this study found highly significant differences in TSH levels in G2 as compared to G3.

Correlation coefficients (r) and p-values for RBP4 with PGRN, BMI, FBG, HbA1C%, TT3, TT4, and TSH were shown in Table 2. Results showed a highly significant correlation for RBP4 with PGRN, BMI, FBG, HbA1C%, TT3, TT4, and TSH in G1, G2, and G3. In addition to a highly significant association between PGRN with RBP4, BMI, FBG, HbA1C%, TT3, TT4, and TSH in G1, G2, and G3 were found in Table 3.

DISCUSSIONS

In this study, there was a strong correlation between RBP4 with FSG, HbA1C, TT3, TT4 levels in hypothyroidism and hyperthyroidism patients; therefore, these patients may be at risk of diabetes; also, there was a decrease in RBP4 level in thyroid dysfunction patients comparing with control. These results agreed with the Zemany and *et al*. study, which proved the levels of RBP4 in combination with free testosterone and TSH in the postmenopausal female. RBP4 and the thyroid hormone, thyroxine (T4), are transferred through the blood by transthyretin (TTR), a protein transporter.[24] The protein complex, forming by binding RBP4 with TTR, blocks glomerular filtration and decreases RBP4 renal clearance. Thus, by promoting its renal clearance, reducing TTR could decrease circulating levels of RBP4.[16] Overall, the relationship between RBP4 in patients of Chinese ethnicity with glucose metabolism, oxidative stress, and thyroid function are correlated. The patients showed increased glucose metabolism and decreased RBP4 levels after laparoscopic sleeve gastrectomy (LSG) surgery in the 3rd and 6th months. Their study also indicates that decreased levels of RBP4 may partially account for improved glucose metabolism after LSG in obese patients.RBP4 levels had a strong positive association with TSH in obese individuals. The alteration in the level of serum RBP4 was correlated with an alteration in TSH in males in the third month following LSG. Therefore, they suggest that RBP4 in obesity can play a role in thyroid dysfunction.[25]

The current study was opposite other studies; the study by *Nearmeen and et. al.* provide evidence of higher levels of serum RBP4 in hypothyroidism, especially in patients with ischemic stroke (IS), associated with metabolic and glucose abnormalities, and, thus, it could be a promising predictive biomarker of IS in hypothyroidism.[26] Also the study by Kokkinos and *et al*. has been demonstrated that the RBP4 level is higher in clinical hypothyroidism patients than in controls. In hypothyroidism, the RBP4 level was increased independently of obesity in elderly participants with normal glucose tolerance. Serum RBP4 levels were found to be considerably higher in clinical and subclinical hypothyroid (SCH). However, the data on the association of RBP4 with thyroid dysfunction are very limited. Now, they have proved that serum RBP4 level was raised and positively linked to TSH level in patients with SCH. These results are in line with prior studies showing that patients with subclinical and overt hypothyroidism have higher levels of circulating RBP4 than those with healthy thyroid

Table 2: Correlation coefficients (r) and p-values between RBP4 with PGRN, BMI, FBG, HbA1C, TT3, TT4, and TSH in G1, G2, and G3.

	RBP4		
Parameters	*r1/p-value*	*r2/p-value*	*r3/p-value*
PGRN	*0.464* *HS*	*0.087* *HS*	*0.527* *HS*
BMI	*0.105* *HS*	*-0.291* *S*	*0.102* *S*
FBG	*0.104* *HS*	*0.478* *HS*	*0.005* *HS*
HbA1C	*0.016* *HS*	*0.145* *HS*	*0.429* *HS*
TT3	*0.307* *HS*	*-0.234* *HS*	*-0.390* *HS*
TT4	*0.559* *HS*	*0.044* *HS*	*0.337* *HS*
TSH	*- 0.671* *HS*	*-0.642* *S*	*-0.479* *HS*

S: Significant ($p < 0.05$), HS: Highly significant ($p < 0.001$), NS: Non-Significant ($p \geq 0.05$).

Table 3: Correlation coefficients (r) and p-values between PGRN with RBP4, BMI, FBG, HbA1C, TT3, TT4, and TSH in G1, G2, and G3.

	PGRN		
Parameters	*r1/p-value*	*r2/p-value*	*r3/p-value*
RBP4	*0.464* *HS*	*0.087* *HS*	*0.527* *HS*
BMI	*-0.210* *HS*	*-0.562* *HS*	*-0.131* *HS*
FBG	*0.452* *HS*	*-0.183* *S*	*0.169* *S*
HbA1C	*-0.163* *HS*	*-0.562* *HS*	*-0.060* *HS*
TT3	*0.413* *HS*	*-0.161* *HS*	*0.028* *HS*
TT4	*0.567* *HS*	*-0.186* *HS*	*0.200* *NS*
TSH	*-0.064* *HS*	*0.010* HS	-0.462 HS

S: Significant ($p < 0.05$), HS: Highly significant ($p < 0.001$), NS: Non-Significant ($p \geq 0.05$).

function.[27] RBP4 participates to T2D pathogenesis. The current results are compatible with prior studies showing that RBP4 is significantly linked to individuals' glucose metabolism.[13] Nonetheless, few studies have investigated the relationship of RBP4 levels with thyroid role in obesity. Also, a previous study found that RBP4 concentration was positively correlated with TSH in postmenopausal females.[28]

Circulating PGRN is substantially associated with diabetes indicators such as BMI, macrophage omental adipose tissue infiltration, the concentration of serum C-reactive protein (CRP), HbA1C, and total cholesterol levels. Additionally, the PRGN serum level has increased in T2 DM patients compared with healthful controls.[29]

In the Chinese population, the association between PGRN and T2 DM, described in the Korean population by Youn *et al.,* Has been demonstrated,[30] and it is not fully known whether PGRN is a cause or a consequence of some disease. PGRN can be involved in the pathogenesis of obesity, T2DM and may become a target for the protection or treatment of metabolic disturbances.[31] In the pathogenesis of diabetes, new signs have been studied, including some adipokines, like PGRN.[32] There is an indicator that PGRN levels are raised in T2DM when correlated to nondiabetic subjects, so, PGRN is strongly associated with glucose metabolism. There is a positive relationship between PGRN with A1C, fasting plasma glucose, and 2 hours post-challenge plasma glucose.[33] In weakness glucose tolerance individuals, elevated in PGRN levels are also observed, revealing its role in prediabetic conditions. Furthermore, a current study estimatingT2DM patients describes that higher levels of PGRN are found in obese individuals.[29]

The Hyemi K., *et al.* study was the first in determining the level of serum PGRN in thyroid cancer patients, known as obesity-related cancer. Nonetheless, there was no important difference in levels of serum PGRN between the benign and papillary thyroid cancer groups. These findings indicated that the level of serum PGRN is possible to be correlated with progression rather than thyroid cancer development.[34] The PGRN expression was raised in serum and aorta of rats with subclinical and clinical hypothyroidism. In vitro, the TSH-catalyzed rise in PGRN resulted in the up-regulation of eNOS by Akt signaling pathway in HUVECs. Akt plays a significant role in mediating TSH acts in the thyroid. In TSH mediating eNOS, this pathway was also very significant. In the SCH, endothelial dysfunction occurs, and PGRN is shared in the TSH up-regulating eNOS expression mechanism in the endothelium via the Akt pathway. Though TSH decreased the synthesis of NO, this meaning uncoupled eNOS, which led to endothelial dysfunction.[35]

The link between thyroid disorders and diabetes mellitus is distinguished via a complicated linked reaction. Insulin resistance conditions may be raise in thyroid gland nodularity, and coexisting diabetes may raise the danger of visual loss in Graves' disease patients. Hyperthyroidism in diabetic patients weakens glycemic regulation, whereas hypothyroidism can elevate susceptibility to hypoglycemia, thereby complicating the management of diabetes.[36] Thyroid hormones are the chief regulators of metabolic processes. They directly influence insulin secretion, insulin sensitivity, carbohydrate metabolism, and blood glucose by interacting with different organs like the liver, skeletal muscles, adipose tissue, and pancreas.[37]

In the case of hypothyroidism, there is decreased hepatic glucose production via glycogenolysis and gluconeogenesis. Insulin synthesis and release are also reduced in hypothyroidism. Further, hypothyroidism-induced receptor defect has also been proposed to be a possible mechanism for decreased insulin-mediated peripheral utilization of glucose. All these increases the risk of recurrent hypoglycemia in diabetic patients.[38]

A decrease in the rate of intestinal glucose absorption occurs in a hypothyroidism state, besides a reduction in adrenergic activity resulting in a decrease in liver and muscle glycogenolysis, also, a reduction in gluconeogenesis and secretion of baseline insulin. However, there has been a rise in insulin secretion after eating against the backdrop of generalized peripheral insulin resistance correlated with a high concentration of free fatty acid, decreased glucose absorption, and raised oxidation of glucose.[39]

In hyperthyroidism, there is an increase in insulin resistance and the production of glucose. Hyperthyroidism stimulates the endogenous production of glucose. Though hyperthyroidism is linked with insulin resistance, it is shown to increase the secretion of insulin. However, in hyperthyroidism, the insulin is secreted as an inactive precursor, which is rapidly degraded, causing a reduction in insulin half-life.[40] A major rise in the amount of tissue metabolism is involved in the condition of hyperthyroidism. To adjust to the greater energy loss, the rate of cellular glucose depletion, both baseline and insulin-stimulated, raises further intense glucose oxidation and lactic acid production, which is later used by the liver to speed up gluconeogenesis and endogenous glucose production.[41]

CONCLUSIONS

The present study is the first to shed light on the relationship between PGRN and thyroid disorder, which provides a guide on the increase in PGRN levels of patients with a thyroid disorder, especially in patients with hyperthyroidism, related to metabolic and glucose abnormalities, and then, it may be a trustable predictive biomarker for detection early stage of diabetes mellitus type 2 in patients with a thyroid disorder. Also, there was a significant correlation between RBP4 and PGRN in these patients. In addition, these patients with hyperthyroidism were more likely to diabetes than patients with hypothyroidism.

REFERENCES

1. Crunkhorn S, Patti ME. Links between thyroid hormone action, oxidative metabolism, and diabetes risk. Thyroid. 2008; 18(2): 227–237.
2. Brent GA. Mechanisms of thyroid hormone action. *J Clin Invest.*2012; 122(9): 3035–3043.
3. Brent GA. Clinical practice. Graves' disease. N Engl J Med.2008; 358(24): 2594–2605.

4. Brent GA, Davies TF. Hypothyroidism and thyroiditis. In: Melmed SP, Larsen PR, Kronenberg HM, eds. Williams Textbook of Endocrinology. 10th ed. Philadelphia, Pennsylvania, USA: Elsevier; 2012;406-439.
5. Núñez A, Bedregal P, Becerra C, Grob L. Neurodevelopmental assessment of patients with congenital hypothyroidism. Rev Med Chil. 2017;145(12):1579-1587.
6. Luo L, Lü L, Lu Y, Zhang L, Li B, Guo K, et al. Effects of hypoxia on progranulin expression in HT22 mouse hippocampal cells. Mol Med Rep. 2014; 9(5):1675-1680.
7. Wei Z, Huang Y, Xie N, Ma Q. Elevated expression of secreted autocrine growth factor progranulin increases cervical cancer growth. Cell Biochem Biophys.2015;71(1):189-193.
8. Abella V, Pino J, Scotece M, Conde J, Lago F, Gonzalez-Gay MA, et al. Progranulin as a biomarker and potential therapeutic agent. Drug Discov Today. 2017;22(10):1557-1564.
9. Sutton BS, Langefeld CD, Campbell JK, Haffner SM, Norris JM, Scherzinger AL, et al. Genetic mapping of a 17q chromosomal region linked to obesity phenotypes in the IRAS family study. Int J Obes.2006;30(9):1433-1434.
10. Fradin D, Heath S, Lathrop M, Bougneres P. Quantitative trait loci for fasting glucose in young Europeans replicate previous findings for type 2 diabetes in 2q23-24 and other locations. Diabetes. 2007;56(6):1742–1745.
11. Sun HX, Ji H, Chen XL , Wang Li, Wang Y, Shen XY, *et al*. Serum retinol-binding protein 4 is associated with the presence and severity of coronary artery disease in patients with subclinical hypothyroidism. AGING. 2019;11(13):4510-4520.
12. Majerczyk M, Olszanecka-Glinianowicz M, Puzianowska-Kuznicka M, Chudek J. Retinol-binding protein 4 (RBP4) as the causative factor and marker of vascular injury related to insulin resistance. Postepy Hig Med Dosw.2016;70(0):1267–1275.
13. Yang Q, Graham TE, Mody N, Preitner F, Peroni OD, Zabolotny JM, et al. Serum retinol binding protein 4 contributes to insulin resistance in obesity and type 2 diabetes. Nature. 2005;436(7049):356–362.
14. Mohapatra J, Sharma M, Acharya A, Pandya G, Chatterjee A, Balaraman R, Jain MR. Retinol-binding protein 4: a possible role in cardiovascular complications. Br J Pharmacol.2011; 164(8):1939–1948.
15. A.F. AL-Taie, Warka'a T. Saloum, and Forat Yahya Mohsin Shabil. Correlation study of retinol binding protein-4, nesfatin and thyroid hormones in colorectal male patients.Plant Archives.2020; 20(1): 2841-2846.
16. Zemany L, Bhanot S, Peroni OD, Murray SF, Moraes-Vieira PM, Castoldi A, et al. Transthyretin antisense oligonucleotides lower circulating RBP4 levels and improve insulin sensitivity in obese mice. Diabetes 2015; 64(5):1603–1614.
17. Li F, Xia K, Sheikh MS, Cheng J, Li C, Yang T. Retinol binding protein 4 promotes the hyperinsulinism-induced proliferation of rat aortic smooth muscle cells. Mol Med Rep.2014; 9(5):1634–1640
18. LiuY,ZhongY,ChenH,WangD,WangM,OuJS,XiaM.Retinol-binding protein dependent cholesterol uptake regulates macrophage foam cell formation and promotes atherosclerosis. Circulation 2017; 135(14):1339–1354
19. Al-Jowari S. Comparative Investigation of thyroid autoantibodies between type 1 and type 2 diabetes mellitus patients in Baghdad City. Iraqi Journal of Science. 2017;58(2B):815-819.
20. Kalra S, Aggarwal S, Khandelwal D.Thyroid Dysfunction and Type 2 Diabetes Mellitus: Screening Strategies and Implications for Management. Diabetes Ther.2019; 10(6):2035–2044.
21. Gu Y, Li H, Bao X, Zhang Q, Liu L, Meng G, et al. The relationship between thyroid function and the prevalence of type 2 diabetes mellitus in euthyroid subjects. J Clin Endocrinol Metab. 2017;102(2):434–442.
22. Goldstein DE., Little RR., Lorenz RA., Malone JI., Nathan D., Peterson CM. Tests of glycemia in diabetes. Diabetes Care.1995; 18(3):896-909.
23. Massod, M. F. Nonparametric percentile estimate of clinical normal ranges. Am J Med Technol.1977; 43(3), 243-252.
24. Zanotti G, Berni R. Plasma retinol-binding protein: structure and interactions with retinol, retinoids, and transthyretin. Vitam Horm. 2004;69:271–295.
25. Wang X, Huang Y, Gao J,Sun H, Jayachandran M, Qu Sh. Changes of serum retinol-binding protein 4 associated with improved insulin resistance after laparoscopic sleeve gastrectomy in Chinese obese patients. Diabetol Metab Syndr.2020; 12(7):1-10.
26. Rashada NM, Sabryb HM, Afifia SA, Fathyc MA, El-Helalyd AM, Mohamede HE. Serum retinol-binding protein 4 and the risk of ischemic stroke in Egyptian patients with hypothyroidism. Egypt J Intern Med. 2019; 31(4):746–753.
27. Kokkinos S, Papazoglou D, Zisimopoulos A, Papanas N, Tiaka E, Antonoglou C, Maltezos E. Retinol Binding Protein-4 and Adiponectin Levels in Thyroid Overt and Subclinical Dysfunction. Exp Clin Endocrinol Diabetes. 2016; 124(2):87–92.
28. Güdücü N, Görmüş U, Kavak ZN, İşçi H, Yiğiter AB, Dünder İ. Retinolbinding protein 4 is elevated and is associated with free testosterone and TSH in postmenopausal women. J Endocrinol Invest. 2013;36(10):831–834.
29. Qu H, Deng H, Hu Z. Plasma progranulin concentrations are increased in patients with type 2 diabetes and obesity and correlated with insulin resistance. Mediators Inflamm. 2013; 2013:360190.
30. Youn BS, Bang SI, Klöting N, Park JW, Lee N, Oh JE. Serum progranulin concentrations may be associated with macrophage infiltration into omental adipose tissue. Diabetes. 2009; 58(3):627–636.
31. Nicoletto BB, Canani LH. The role of progranulin in diabetes and kidney disease. Nicoletto and Canani Diabetol Metab Syndr.2015; 7:117.
32. Dunmore SJ, Brown JE. The role of adipokines in beta-cell failure of type 2 diabetes. J Endocrinol. 2013;216(1):37–45.
33. Li H, Zhou B, Xu L, Liu J, Zang W, Wu S, Sun H. Circulating PGRN is significantly associated with systemic insulin sensitivity and autophagic activity in metabolic syndrome. Endocrinology. 2014;155(9):3493–3507.
34. Kwon H, Park SE, Yun JS, Park CY. Serum Adiponectin and Progranulin Level in Patients with Benign Thyroid Nodule or Papillary Thyroid Cancer. Endocrinol Metab. 2020; 35 (2):396-406.
35. Jiang F, Wang H, Bao S, Zhou H, Zhang Y, Yan Y, et al. Thyrotropin Regulates eNOS Expression in the Endothelium by PGRN Through Akt Pathway. Front. Endocrinol. 2018;9: 353.
36. Hage M, Zantout MS, Azar ST. Thyroid Disorders and Diabetes Mellitus. J Thyroid Res 2011; 2011: 439463. doi: 10.4061/2011/439463.

37. Mullur R, Liu YY, Brent GA. Thyroid Hormone Regulation of Metabolism. Physiol Rev. 2014;94(2):355-382.
38. Falzacappa VC, Mangialardo C, Raffa S, Mancuso A, Piergrossi P, Moriggi G, et al. The thyroid hormone T3 improves function and survival of rat pancreatic islets during in vitro culture. Islets 2010;2(2):96-103
39. Maratou E, Hadjidakis DJ, Kollias A , Tsegka K, Peppa M, Alevizaki M, et al. Studies of insulin resistance in patients with clinical and subclinical hypothyroidism. Eur J Endocrinol 2009; 160(5): 785–790.
40. Dimitriadis G, Raptis SA. Thyroid hormone excess and glucose intolerance. Exp Clin Endocrinol Diabetes 2001;109(2):225-39.
41. Maratou E, Hadjidakis D, Peppa M, Alevizaki M, Tsegka K, Boo L. Studies of insulin resistance in patients with clinical and subclinical hyperthyroidism. Eur J Endocrinol 2010; 163(4): 625–630.