Received: 08 August 2021 | Revised: 09 September 2021 | Accepted: 18 September 2021
DOI: 10.22034/ecc.2021.298959.1210
Eurasian Chemical Communications
SAMI

FULL PAPER

Evaluation of the osteoprotegerin and insulin levels in patient's serum with hypothyroid and hypothyroid with type 2 diabetes mellitus

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The aim of this study: to estimate OPG levels in serum of patients with thyroid disorder and thyroid disorder + type 2 diabetics and the relationship between them. The study was conducted on 105 subjects and they were divided into three groups with these inclusion criteria: 70 thyroid disorders and thyroid diabetes patients (female) and 35 healthy controls. The age range was 18 –45 years. The parameters which have been measured include:-Age, BMI, TT3, TT4, TSH, FBS, Insulin hormone, HOMA-IR and those of the lipid function test. COL, Tg, HDL, VLDL, and LDL. Our results support that hypothyroidism is not the main reason for type 2 diabetes mellitus, but the altered lipid profile in hypothyroid patients is the main implicated in incidence of prediabetes, which represents HOMA-IR resistance and risk for development of type 2 diabetic mellitus. Conclusion Depending on the results obtained during this study, the increase in osteoprotegrine levels in hypothyroid and hypothyroid + type 2 DM is not related to these diseases. In other words, OPG is not legitimately ensnared in hypothyroidism or type 2 diabetic mellitus pathogenesis. Moreover, the disorders in lipid profile levels were legitimately ensnared in hypothyroidism which develops.

KEYWORDS

Osteoprotegrin; insulin, lipid disorder; thyroid disorder; hypothyroidism; type Π diabetes mellitus.

Introduction

The most prevalent endocrine illnesses are thyroid disease and diabetes. The first research demonstrating a link between them was published in 1979, and a number of subsequent studies revealed that thyroid dysfunction is common among diabetes patients. Thyroid function tests are indicated for patients with clinical suspicion or unexplained changes in diabetic metabolic control, serum cholesterol, or weight gain, because thyroid dysfunction can cause significant metabolic disturbances (Al Haj & Qasim, 2013). Autoimmune disorder patients are more likely to develop additional autoimmune disorders. Thyroid hormones and insulin interact together in body cells to affect metabolism; any change in one of these might affect metabolism and disrupt glucose homeostasis (Mohsin, 2021). Diabetes mellitus was also seen in both hypothyroid and hyperthyroid patients. Autoimmunity can interpret the common association between T1DM and autoimmune thyroid diseases, but the linkage between T2DM and TD is more complicated (Ighewish *et al.*, 2020). Also, thyroid dysfunction can result in lipid disturbances as well as the composition and transport of lipoproteins is one of the abnormalities in thyroid diseases (Dixit *et al.*, 2020). For the same amount of insulin

resistance and despite having a higher level of low-grade chronic inflammation, individuals with AITD and pre-diabetes have a superior - cell insulin secretory profile than patients without AITD, according to a study. This could simply imply that thyroid autoimmunity has no effect on cell secretory function. (Alexandraki *et al*., 2020).

Osteoprotegerin is a soluble member of the tumor necrosis factor receptor superfamily that plays a role in the activation of nuclear factor kappa B (NF-kB) ligand (RANKL)-mediated osteoblastic bone resorption (Hur *et al*., 2018).

Thyroid deficiency reduces skeletal growth due to lower levels of growth hormone and insulin growth factor, and in children with thyrotoxicosis, osteoblastic activity is reduced (Raman, P. 2018). T4 and T3 are essential for development and differentiation of human body cells and for prevention of bone loss in adult bone (Sarah *et al*., 2019). This study is designed to show the estimation of osteoprotegrine in thyroid disorder and thyroid disorder with type 2 diabetes mellitus and the relationship between them.

Methods and material

The study was conducted on **105** subjects divided into three groups: Group I: - 35 patients with thyroid with medication; Group II: - 35 patients with thyroid disorder and diabetes type 2 with medication; and Group III: - 35 for healthy individuals as the control group.

Blood was collected by serum gel tube according to inclusion criteria of the study: 70 thyroid disorders and thyroid diabetes patients (female) and 35 healthy controls. The age range was 18 –45 years. Included in the study were cases with medication. They were recruited from the National Diabetes Center of AL-Mustansira University. A study protocol was applied to each patient and the control groups. A personal approval was taken from each patient as well as the control groups. The diagnosis of patients was carried out by an endocrinologist and with exclusion criteria, i.e., the patients suffering from any other chronic diseases, or having high ESR levels, hyperthyroid disorder, typ1 DM and the pregnant women. The parameters which were measured included age, BMI, TT3, TT4, TSH, FBS, Insulin hormone, HOMA-IR and those of the lipid function tests, Chol, Tri, HDL, VLDL, and LDL. The analysis test of FBG, lipid profile, TSH, T3 and T4 levels was determined automatically by COBAS C111 and Cobas e411 analyzers. HOMA-IR was calculated by the following equation: HOMA-IR= FBG x INSULINE 405 (Gopalakrishnan, 2020). OPG and INS were determined by the ELISA sandwich technique (enzyme-linked immunosorbent assay). The data was gathered, scored, and analyzed using the Statistical Package for Social Science (SPSS) version 20.00. Continuous variables were provided as means with standard deviation, while categorical variables were reported as frequency and percentages. To compare between two means and SD, we used the t-test and to compare more than two means and SD, we used analysis of variance (ANOVA). The linear link between the variables was determined using correlations (Kim, 2017).

Results and discussion

The results showed high significant differences (P 0.01) between patient groups in age; the highest was in thyroid with diabetes type II (43.800 8.509) and the results of BMI were significantly different (P 0.05) between thyroid with diabetes type II and control subjects; the highest result was recorded with thyroid disorder with diabetes mellitus (34.394 6.547). TSH hormone levels were higher in the group of patients who had thyroid disorder with diabetes mellitus (4.02 0.51) than in control subjects. T3 hormone levels were higher in both groups of the patients than those in the control group (P 0.01). The highest result was recorded in the

healthy group with (124.83817.798). There were high significant differences (P 0.01) between patients' groups and control subjects in TG levels; the highest was in thyroid with diabetes type II (227.19 22.90). There were high statistical differences (P 0.01) between thyroid disorder with DM group and thyroid disorder and control group in both FBS and HOMA-IR as documented. There were high statistical differences (P 0.01) between the thyroid disorder with the DM group with (15.927 4.891) and the thyroid disorder with (29.66 3.28) and between the thyroid disorder and the control group with (10.548 2.165) in insulin levels. Finally, the Osteoprotegrin levels showed high statistical differences between the thyroid and thyroid with diabetes groups and between the thyroid and healthy groups as follows: (58.692 13.444) (69,954 13.234) and (35.146 8.598), respectively (Table 1). Diabetes mellitus was also seen in both hypothyroid and hyperthyroid patients. Autoimmunity can interpret the common association between T1DM and autoimmune thyroid diseases, but the linkage between T2DM and TD is more complicated (Ighewish *et al*., 2020). Numerous studies have mentioned this relationship. One of these studies (Karunanidhi & Gunasekaran, 2018) compared diabetic patients with normal patients. The prevalence of altered thyroid profile in the study group was high, with hypothyroidism being the most common. Another study suggested thyroid function may impact the development of insulin resistance and type 2 DM when they found a positive and linear association between TSH levels within the reference range and HOMA-IR in both non-DM subjects and type 2 DM patients, especially in patients with high HbA1c levels (Zhu *et al*., 2018). It is a good way to start the day.

The subjects in T2DM study group had significantly higher serum (LDL and TG) than non-diabetic study subjects, and low thyroid function was positively associated with lipid dysregulation in patients with type 2 diabetes mellitus. Patients with type 2 diabetes mellitus had significantly lower T3 and T4 and higher TSH. Furthermore, substantial positive connections existed between TSH and LDL and TG, as well as significant negative correlations between TG and T4 and T3 (Jiffri, 2017). Further, based on a study conducted to compare hypothyroidism patients with the normal thyroid group, the results demonstrated a significant increase in LDL, VLDL, and TG levels in hypothyroidism patients (Aati & Al-Ali, 2020). It is expected that patients with hypothyroidism live in a pre-diabetic state. Beta cells at this stage secrete large amounts of insulin to reduce blood glucose levels and insulin resistance. However, there was a correlation between triglycerides, low density lipoprotein and insulin, HOMA-IR. This agrees with a study that reported that diabetes has a significant role in alteration of lipoprotein levels. All the lipid profile parameters were significantly increased except HDL among the patients with diabetes (Padhy, 2019), which agrees with our results, showing the results of analysis of symptoms of insulin resistance of the insulin levels in the thyroid group were higher than those in the thyroid disorder + type 2 DM (15.927 4.891) and high levels in HOMA-IR in both groups, while the thyroid group recorded lower levels (7.3625.207) in HOMA-IR compared with the thyroid disorder with DM (7.5063.694). The results showed that the thyroid group coexists with prediabetes because their pancreatic beta-cells are still able to increase their production of insulin to try to prevent insulin resistance and maintain lower glucose levels in the blood. The results of hyperglycemia parameters correlation showed HOMA-IR had a statistically significant positive correlation with FBG, INS, Tri, and LDL in thyroid patients and also correlated positively with FBG, INS. But there was no correlation between FBS, INS, HOMA-IR with TSH, T3, T4 in cases. This may be owing to the effect of metformin treatment where there was lower TSH levels in thyroid with DM patients, in both hypothyroid and

euthyroid disorders respectively, compared with thyroid patients with non-DM. This agrees with the clinical evidence that metformin has TSH lowering effects in patients with T2DM and hypothyroidism or in those with TSH serum levels in the upper normal value (Cannarella *et al*., 2020). In a study, OPG was found to be a marker of insulin sensitivity and atherogenic risk. It is correlated positively with HDL and HOMA-IR, and it is negatively correlated with LDL (Ayina *et al*., 2015). This agrees with the study suggesting type 2 DM with SCH patients demonstrate increased levels and independent association with serum OPG (significantly higher HOMA-IR, serum TSH) than those with euthyroid (El-Adawy *et al*., 2017). In the present study, there was no correlation between OPG serum level and any other variables in patients' groups and control group, although there was a highly significant statistical difference between serum OPG levels in thyroid patients than in thyroid with DM and a high significant statistical difference compared between cases and the control group. There are reasons put forward to account for our results, such as the duration of thyroid and diabetes mellitus diseases and the complications of diabetic mellitus; any chronic and inflammatory diseases were excluded from this study criteria, as well as the presence of the normal reference of TSH and thyroid hormone levels in hypothyroidism patients as a result of medications used. Also, in agreement with past findings, in OHT and SHT, the plasma OPG levels before therapy were significantly higher than after normalization of thyroid function with treatment, where OPG levels in both groups decreased markedly. The absolute changes in OPG showed a significant positive correlation with the changes in TSH (Xiang *et al*., 2007) and this corresponds with the fact that most subjects in our study were undergoing treatment with levothyroxine hormone and the T3, T4 were mostly the same. The individuals in this study were young to adults compared with the previously conducted studies that included older adults, and this is consistent with the evidence in some studies, as an instance, the finding that in postmenopausal women with diabetes and pre-diabetes, the serum OPG level was associated with IR (Duan *et al*., 2017).

Finally, our results support that hypothyroidism is not the main reason for type 2 diabetes mellitus, but the altered lipid profile in hypothyroid patients is mainly implicated with incidence of prediabetes, which represents HOMA-IR resistance and risk for development of type 2 diabetes mellitus due to the hypothyroid causes of slowing down the metabolism, resulting in a decrease in insulin levels without a decrease in insulin levels.

TABLE 1 Parameters of the study among groups

	Healthy control (m±SD) (n=35)	Thyroid patients (m±SD) (n=35)	Thyroid+DM patients (m±SD) (n=35)	ANOVA (F value) (Significance)
AGE (year)	34.143±10.937	33.934±8.842	43.800±8.509	12.32638**(b, c)
BMI (Kg/m2)	29.659±6.541	31.812±8.487	34.394±6.547	3.74204*(b)
TSH (µIU/mL)	1.802±1.014	2.897±0.60	4.02±0.51	5.62105*(b)
T3 (ng/dl)	124.838±17.798	122.252±42.567	100.406±34.573	5.664*
T4 (µg/dl)	8.717±1.454	9.093±3.667	7.930±2.706	1.61578***
Chol. (mg/dl)	177.851±28.718	177.570±38.445	186.951±58.840	0.5188***
Tri. (mg/dl)	134.154±22.750	155.687±43.471	227.19±22.90	11.99186**(b, c)
HDL (mg/dl)	44.392±10.606	39.038±11.463	39.706±13.125	2.1477***
VLDL (mg/dl)	27.678±5.500	84.212±23.062	48.437±33.454	51.0745***(a, b)
LDL (mg/dl)	79.720±13.024	31.806±8.703	88.113±23.033	124.878***(a, b, c)
FBS (mg/dl)	85.856±9.525	98.800±8.702	193.09±15.28	43.1175**(a, c)
INSULIN (µIU/ml)	10.548±2.165	29.66±3.28	15.927±4.891	25.07869**(b, c)
HOMA-IR	2.230±0.467	7.362±5.207	7.506±3.694	23.13921**(b, c)
OPG(pg/ml)	35.146±8.598	69.954±13.234	58.692±13.444	77.06729**(a, b, c)

Conclusion

Relying on the results obtained in this study, the increase in osteoprotegrine levels in hypothyroid and hypothyroid + type 2 DM is not related to these diseases. In other words, OPG is not legitimately ensnared in hypothyroidism or type 2 diabetes mellitus pathogenesis, yet they might be included as cytokines, influenced by age, complications of diseases, and chronic diseases. Moreover, the disorders in lipid profile levels were legitimately ensnared in hypothyroidism, which is a developing risk for type 2 diabetes mellitus since the obesity, lipid and HOMA-IR are listed under the syndrome metabolic.

Acknowledgements

First of all, I would like to thank "Allah" for all the success in my life and for facilitating the ways to achieve my dreams and ambitions to it become reality.

I would like to express my special thanks and gratitude to my supervisor, Prof. Dr. Sanad Baqir Mohammed, for his support and guidance throughout my MSc. Thank you for your confidence in my abilities. I am forever grateful and proud for having had the opportunity to work with you.

I would like to express to my endless thanks to my co-supervisor, consultant physician Specialty Prof. Tawfeeq F.R. Al-auqbi\ M.B.Ch.B PhD for his assistance and guidance to complete my thesis in full.

Also my thanks to the staff members of The National Diabetes Center (NDC) \ Mustansiriya University, in Baghdad. My sincere thanks and appreciation to all thyroidism and diabetic patients at the Diabetes Center for their help in this work with my wishes and prayers for all patients by health and safety.

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How to cite this article: Jwan Najm Abdullah*, Sanad Baqir Mohammed, Tawfeeq F.R. Al-auqbi. Evaluation of the osteoprotegerin and insulin levels in patients serum with hypothyroid and hypothyroid with type 2 diabetes mellitus. *Eurasian Chemical Communications*, 2021, 3(11), 854-859. **Link:** http://www.echemcom.com/article_138606.html