Visfatin, PON-1 Levels in Iraqi Hyperthyroidism Patient's with Dyslipidemia

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Abstract In the study, it is aimed to research the likely role of visfatin in hyperthyroid and subclinical hyperthyroid status related to dislipidemia, after determining the visfatin and PON-1 levels thirty healthy individuals were enrolled in this study as control group and thirty hyperthyroidism patient's with dyslipidemia they were treated with. The subjects aged ranged (30–50) years and with BMI (25–29) kg/m². Serum was used in determination of lipid profile total cholesterol (TC), triglyceride (TG), high density lipoprotein (HDL), low density lipoprotein (LDL), very low density lipoprotein (VLDL), thyroid threonine (T3) and thyroxine (T4), thyroid stimulating hormone (TSH), visfatin and paraoxonase-1 (PON-1). The results showed significant increase in T3, T4, TC, TG, LDL and VLDL in patient group when comparing to control group. While significant decrease was found in TSH and HDL in patient group when comparing to control group. The results also represented significant increase in visfatin levels in patient group comparing to control group. While there are significant reduction in PON-1 levels in patient group comparing to control group. The conclusion could be drawn from this study that visfatin and PON-1 effected hyperthyroidism patient's with dyslipidemia All the patients in hyperthyroid group were heterozygotes for Familial Hypercholesterolemia is a disorder that is passed down through families. It causes LDL (bad) cholesterol level to be very high. The condition begins at birth and can cause heart attacks at an early age.

Keywords Hyperthyroidism patient's with dyslipidemia · Visfatin · PON-1

Introduction

The production of thyroid hormones (T3 and T4) is tightly regulated by the secretion of thyroid stimulating hormone (TSH; also known as thyrotropin) from the pituitary gland in the brain. The production or release of thyroxine and triiodothyronine can be abnormally high, leading to hyperthyroidism. The TSH level in the blood almost always becomes suppressed, because the pituitary gland senses the abnormally high levels of thyroid hormones, which are more than is needed by the brain [1, 2].

Hyperthyroidism induces a hyperdynamic cardiovascular state that is associated with tachycardia, systolic hypertension, atrial fibrillation, and increased cardiovascular mortality. Thyroid hormones influence lipid metabolism, including synthesis, mobilization, and degradation [3]. Dyslipidemia is an increase in the cholesterol, triglycerides and lipoproteins [4].

Visfatin is an adipocytokine produced predominantly by the visceral fat with molecular weight of 52 kDa. It has in its structure 491 amino acid residues. Visfatin has an expression in hepatocytes, muscles adipocytes, kidneys and heart [5, 6]. In some studies it was reported that visfatin is strongly expressed in foam cells in atherosclerotic lesions with the increase of expressivity, especially in atheroma plaques in symptomatic plaques [7].

Paraoxonase-1 (PON-1) is an antioxidant enzyme that hydrolyzes lipid peroxides in oxidized lipoproteins. PON-1 activity has been suggested to be inversely associated with oxidative stress in serum and macrophages [8, 9]. PON-1 is synthesized in the liver and transported along with HDLs in

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the plasma which closely attached to HDL particles by apolipoprotein A [10]. PON-1 inhibits oxidation of low density lipoproteins, hydrolysis lipid peroxidation products and involved in decreasing superoxide ion formation. Its serum concentration is influenced by inflammatory changes and the levels of serum oxidized low density lipoproteins [11]. PON-1 can exert a protective effect on HDL by preventing it from lipid peroxidation and reactive oxygen species (ROS) pathogenesis under oxidative stress, such as asthma in children or iron deficiency anemia during pregnancy [12, 13]. There are limited studies about visfatin and PON-1 levels in hyperthyroidism: patient's with dyslipidemia, therefore the present study was aimed to determined the serum visfatin and PON-1 level's in these patient's as a predictor to cardiovascular disease and oxidative state.

Materials and Methods

Thirty healthy individuals as control group and thirty hyperthyroidism with dyslipidemia were enrolled in this study with aged ranged (30–50) years and BMI (25–29) kg/m². Fasting blood samples were collected from all group, and serum that obtained were stored until used for analysis. (TC, TG, HDL) were determine according to the procedure of the hospital laboratory. LDL-C and VLDL were calculated from Friedewald equation [14]:

$$\text{LDL-c(mg/dl)} = \text{Total Cholesterol} - (\text{HDL-c} + \text{VLDL-c}),$$

$$\text{VLDL-c(mg/dl)} = \text{TG}/5 [14].$$

The T3 and T4 were measured using radioimmunoassay from tech company, Belgium. TSH was measured using immunoradio metris assay from Biosource, Nivelles, Belgium. Visfatin and PON-1 were measured by ready kit from (Cuasbo, Ghina) based on ELISA technique [2].

Statistical Analysis

Statistical analysis was performed using statistical package for social science (SPSS) version 13. Data of normal distribution were expressed as mean $\pm$ SD. The significance of differences between the means was carried out by unpaired student's *t* test. The *p* values (*p* > 0.05), (*p* < 0.05), and (*p* < 0.001) were considered statistically non-significant, significant, and highly significant respectively.

Results

The results in Table 1 illustrated the T3, T4, TSH, TC, TG, HDL, LDL and VLDL levels for all studied groups. The results in Table 1 showed significant increase in T3, T4, TC,

Table 1 Levels of T3, T4, TSH and lipid profile for all studied groups

Parameters	Groups		
	Control group	Patient group	<i>t</i> test
T4 (ng/ml)	0.25 $\pm$ 0.07	0.99 $\pm$ 0.02	S
T3 (pg/ml)	0.59 $\pm$ 0.12	2.4 $\pm$ 0.12	S
TSH (μ IU/ml)	1.53 $\pm$ 0.14	0.15 $\pm$ 0.07	S
TG (mmol/L)	0.71 $\pm$ 0.04	3.14 $\pm$ 0.14	S
TC (mmol/L)	3.51 $\pm$ 1.2	6.91 $\pm$ 2.4	S
LDL (mmol/L)	2.1 $\pm$ 0.61	5.49 $\pm$ 0.99	S
HDL (mmol/L)	2.11 $\pm$ 0.9	0.19 $\pm$ 0.03	S

S significant (*p* < 0.05), HS highly significant (*p* < 0.001), NS non-significant (*p* > 0.05)

Table 2 Levels of visfatin and PON-1 for studied groups

Parameters	Groups		
	Control group	Patient group	<i>t</i> test
Visfatin (μ g/ml)	21.6 $\pm$ 7.9	35.8 $\pm$ 6.4	S
PON-1 (ng/ml)	159.9 $\pm$ 35.6	95.7 $\pm$ 20.7	S

S significant (*p* < 0.05), HS highly significant (*p* < 0.001), NS non-significant (*p* > 0.05)

Table 3 Correlation of visfatin levels with some studied parameters in the patient and control group

Parameters	Groups			
	Control group		Patient group	
	r-value	<i>p</i> value	r-value	<i>p</i> value
Vis versus TG	0.381	HS	0.110	HS
Vis versus TSH	– 0.091	HS	0.033	HS

TG, LDL and VLDL in patient group when comparing to control group. While significant decrease was found in TSH and HDL in patient group when comparing to control group.

Table 2 represented the levels of visfatin and PON-1 for studied groups. The results revealed significant increase in visfatin levels in patient group comparing to control group, while there are significant decrease in PON-1 levels in patient group comparing to control group.

Correlation of Visfatin with, TG and TSH

Table 3 shows the results for the correlation of Vis with TG and TSH. There was a significant positive correlation of Vis with TG in the control and patient groups (*r* = 0.381, 0.110). There was a significant negative correlation of Vis with TSH in the control and a significant

Fig. 1 Correlation between visfatin and TG for the control group

Fig. 2 Correlation between visfatin and TG for the patient group

positive correlation in the patient group ($r = -0.091$, 0.033) (Figs. 1, 2, 3, 4).

Correlation of PON-1 with, TG and TSH

Table 4 shows the results for the correlation of PON-1 with TG and TSH. There was a significant positive correlation of PON-1 with TG in the control and patient groups ($r = 0.075$, 0.215).

There was a significant negative correlation of PON-1 with TSH in the control and a significant positive correlation in the patient group ($r = -0.211$, -0.189) (Figs. 5, 6, 7, 8).

Discussion

Thyroid hormones regulate the basal energy expenditure and a hyperthyroid state causes metabolic abnormalities such as dyslipidemia and cardiovascular diseases (CVDs). Thyroid

hormones influence lipid metabolism, including synthesis, mobilization, and degradation [15]. It is well known that alterations in the thyroid function can result in changes in the composition and in the transport of lipoproteins. Specifically, the thyroid hormone stimulates the hepatic de novo cholesterol synthesis by inducing the 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase that catalyzes the conversion of HMG-CoA to mevalonate, which is the first step in the biosynthesis of cholesterol. Additionally, thyroid hormones activate the low-density lipoprotein (LDL) receptors. The promoter of the LDL receptor gene contains a thyroid hormone responsive element (TRE) which allows T3 to up regulate the gene expression of the LDL receptor. Moreover, thyroid hormones stimulate the cholesteryl ester transfer protein (CETP), an enzyme which transports cholesteryl esters from HDL2 to the VLDL and TG in the opposite direction. Finally, thyroid hormones stimulate the lipoprotein lipase which catabolizes the triglyceride-rich lipoproteins and the hepatic lipase, which hydrolyzes HDL2 to HDL3 [16].

Fig. 3 Correlation between visfatin and TSH for the control group

Fig. 4 Correlation between visfatin and TSH for the patient group

Table 4 Correlation of PON-1 levels with some studied parameters in the patient and control group

Parameters	Groups			
	Control group		Patient group	
	r-value	p value	r-value	p value
PON-1 versus TG	0.075	HS	0.215	HS
PON-1 versus TSH	− 0.211	HS	− 0.189	HS

Hyperlipidaemia refers to elevated levels of TG, LDL-c and TC in the blood, and is also identified as dyslipidemia, to describe the manifestations different disorders of lipoprotein metabolism. Although elevated LDL-c is thought to be the best indicator of atherosclerosis risk, dyslipidemia can also describe elevated total cholesterol (Tch) or triglycerides (TG), or HDL-c. Cholesterol has been shown to interrupt and alter vascular structure and

function as it builds within the lining of the vascular wall, and can leading to plaques [17].

Oravec et al. [18] reported, that LDL1 and LDL2 subfractions in hypercholesterolemic individuals which created a non-atherogenic hyper-beta lipoproteinemia LDL1,2 without the presence of atherogenic sdLDL were associated with a high concentration of cardiovascular protective HDL subfractions. TG represent an important biomarker of CVD risk because of their association with atherogenic remnant particles and apoCIII, a proinflammatory, proatherogenic protein found on all classes of the plasma lipoproteins. Hypertriglyceridemic states are associated with increased VLDL production and delayed VLDL clearance from circulation [19]. Small dense LDL tend to be the rule with triglycerides > 1.5 mmol/l and sdLDL particles are usually found in association with high TG and low HDL. The mechanism of this association could be explained by the increased of VLDL formation in elevated TG levels, that result in TG enriched and cholesterol ester depleted LDL particles (with effect of CEPT—cholesterol ester transfer protein). Hepatic lipase then cleaves out the

Fig. 5 Correlation between PON-1 and TG for the control group

Fig. 6 Correlation between PON-1 and TG for the patient group

Fig. 7 Correlation between PON-1 and TSH for the control group

Fig. 8 Correlation between PON-1 and TSH for the patient group

TG leaving cholesterol ester depleted LDL, which are physically smaller and because of resultant relative increase in protein also denser [20]. There is an incidence of adverse effects resulting from either increased or underactive thyroid gland which can lead to higher cardiovascular morbidity and mortality and also overall morbidity. This has been shown in a several cross-sectional and prospectively studies although they were not completely uniform in its conclusions [21].

Study demonstrated that oxidized LDL was verified to increase visfatin expression in cultured monocytes. Moreover, visfatin increased the expression of molecules that degrade extracellular matrix causing plaque instability. This later effect was abolished after adding an inhibitor of insulin receptor signaling [22].

Other study demonstrated that increased visfatin levels are associated to coronary artery disease (CAD) and acute coronary syndromes even after correction for classic cardiovascular risk factors such as cholesterol, smoking, hypertension, diabetes, and obesity [23].

It is well established that acute ischemic stroke is another possible consequence of atherosclerosis which higher visfatin levels were found in Chinese individuals with stroke, suggesting a possible role in this vascular disease [24].

PON1 has antioxidant properties and accounts as a new marker of lipid peroxidation which PON1 prevent the generation of oxidized LDL and inactivates LDL-derived oxidized products when they are formed. PON1 is responsible for anti-atherosclerotic actions of HDL-C, So PON1 levels were inversely associated to the risk of coronary heart disease [25].

It has been reported that hyperthyroidism is associated with a higher risk for ischemic stroke among young adults. Increased production of free oxygen radicals in hyperthyroidism may be responsible for that decrease, or the

decreased PON-1 activity may occur as part of an inflammatory response.

The increase of free T4 levels in hyperthyroidism may cause a decrease in PON-1 activity, this enzyme is involved in decreasing superoxide ion formation. Thus, it is an important antioxidant enzyme with cardioprotective effects. PON-1 inhibits oxidation of low density lipoproteins and also hydrolysis lipid peroxidation products. Its serum concentration is influenced by inflammatory changes and the levels of serum oxidized low density lipoproteins [26].

The conclusion could be drawn from this study that visfatin and PON-1 effected hyperthyroidism patient's with dyslipidemia All the patients in hyperthyroid group were heterozygotes for Familial Hypercholesterolemia (FH) is a disorder that is passed down through families. It causes LDL (bad) cholesterol level to be very high. The condition begins at birth and can cause heart attacks at an early age.

References

1. Murray RK, Bender DA, Botham KM, Kennelly PJ, Rodwell VW, et al. Harper's illustrated biochemistry. 30th ed. New York: Mc Graw Hill Lange; 2017.
2. Shivanada NB. Manipal manual of clinical biochemistry. 3rd ed. New Delhi: Jaypee brothers medical publishers (P) Ltd; 2008.
3. Zhu X, Cheng SY. New insights into regulation of lipid metabolism by thyroid hormone. *Curr Opin Endocrinol Diabetes Obes.* 2010;17:408–13.
4. Reamy BV. Hyperlipidemia management for primary care: an evidence-based approach. 1st ed. New York: Springer; 2009.
5. Garten A, Petzold S, Barnikol-Oettler A, Korner A, Thasler WE, et al. Nicotinamide phosphoribosyl transferase (NAMPT/PBEF/visfatin) is constitutively released from human hepatocytes. *Biochem Biophys Res Commun.* 2010;391(1):376–81.
6. Costford SR, Bajpeyi S, Pasarica M, Albarado DC, Thomas SC, et al. Skeletal muscle NAMPT is induced by exercise in humans. *Am J Physiol Endocrinol Metab.* 2010;98:E117–26.

7. Gligori R, Zdremtan D, Pilat L, Matei I, Ionescu-Tirgoviste C, Crisnic I. Correlations of visfatin with the lipidic metabolism in diabetic and obese patients. *Proc Rom Acad Ser B*. 2012;1:37–43.
8. Mancini A, Festa R, Raimondo S, Pontecorvi A, Littarru GP. Hormonal influence on Coenzyme (Q10) levels in blood plasma. *Int J Mol Sci*. 2011;12:9216–25.
9. Rajkovic MG, Rumora L, Barisic K. The paraoxonase 1, 2 and 3 in humans. *Biochem Med*. 2011;21:122–30.
10. Kilic SS, Aydin S, Kilic N, Erman F, Aydin S, Celik I. Serum arylesterase and paraoxonase activity in patients with chronic hepatitis. *World J Gastroenterol*. 2005;11:7351–4.
11. Bhagwat K. Xanthine oxidase and paraoxonase-I as new markers in the diagnosis and prognosis of organophosphorus pesticide poisoning. *Int J Biol Res*. 2013;1(2):10–4.
12. Shekhanawar M, Shekhanawar SM, Krisnaswamy D, Indumati V, Satishkumar D, et al. The role of ‘paraoxonase-I activity’ as an antioxidant in coronary artery diseases. *J Clin Diagn Res*. 2013;7(7):1284–7.
13. Camuzcuoğlu H, Toy H, Vural M, Camuzcuoğlu A, Taşkın A, et al. Serum paraoxonase and arylesterase activities in iron deficiency anemia during pregnancy. *Turk J Med Sci*. 2011;41:185–91.
14. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative. *Clin Chem*. 1972;81:499–502.
15. Zhu X, Cheng SY. New insights into regulation of lipid metabolism by thyroid hormone. *Curr Opin Endocrinol Diabetes Obes*. 2010;17(5):408–13.
16. Mondal SI, Das SA, Akter A, Hasan R, Talukdar SA, et al. Thyroid hormone and its correlation with age, sex and serum lipid levels in hypothyroid and euthyroid sylheti populations in Bangladesh. *J Clin Diagn Res*. 2011;5(7):1347–51.
17. Gholamhoseinian A, Shahouzehi B, Sharifi-far F. Inhibitory activity of some plant methanol extracts on 3-hydroxyl-3-methylglutaryl coenzyme a reductase. *Int J Pharmacol*. 2010;6(5):705–11.
18. Oravec S, Gruber K, Dostal E, Mikl J. Hyper-betalipoproteinemia LDL 1,2: a newly identified nonatherogenic hypercholesterolemia in a group of hypercholesterolemic subjects. *Neuro Endocrinol Lett*. 2011;32:322–7.
19. Zheng C, Khoo C, Furtado J, Sacks FM. A polipoprotein C-III and the metabolic basis for hypertriglyceridemia and the dense LDL phenotype. *Circulation*. 2010;121(15):1722–34.
20. Abbas JMK, Chakraborty J, Akanji AO, Doi SAR. Hypothyroidism results in small dense LDL independent of IRS traits and hypertriglyceridemia. *Endocr J*. 2008;55:381–9.
21. Biondi B. How could we improve the increased cardiovascular mortality in patients with overt and subclinical hyperthyroidism? *Eur J Endocrinol*. 2012;167:295–9.
22. Saddi-Rosa P, Oliveira CSV, Giuffrida FMA, Reis AF. Visfatin, glucose metabolism and vascular disease: a review of evidence. *Diabetol Syndr*. 2010;2:21.
23. Liu SW, Qiao SB, Yuan JS, Liu DQ. Association of plasma visfatin levels with inflammation, atherosclerosis and acute coronary syndromes (ACS) in humans. *Clin Endocrinol (Oxf)*. 2009;71(2):202–7.
24. Lu LF, Yang SS, Wang CP, Hung WC, Yu TH, et al. Elevated visfatin/pre-B-cell colony-enhancing factor plasma concentration in ischemic stroke. *J Stroke Cerebrovasc Dis*. 2009;18(5):354–9.
25. Goswami B, Tayal D, Gupta N, Mallika V. Paraoxonase: a multifaceted biomolecule. *Clin Chim Acta*. 2009;410(1–2):1–12.
26. Sheu JJ, Kang JH, Lin HC, Lin HC. Hyperthyroidism and risk of ischemic stroke in young adults: a 5-year follow-up study. *Stroke*. 2010;41:961–6.