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Estimation of Visfatin, Adiponectin Hormone and Lipid Profile in Hyperthyroidism Patients

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ABSTRACT

Hyperthyroidism also called Thyrotoxicosis is an abnormal condition occur when the thyroid gland produces and secretes excessive amounts of thyroid hormones, Thyroxine T_4 and Triiodothyronine T_3. This will leads to speed up body metabolic rate, weight loss, and irregularheartbeat. Adiponectin andVisfatin are hormones secreted from the Adipose tissue, which they have an essential role for maintaining glucose, lipid metabolism and energy expenditure.

Eighty sample of both gender between 20 and 60 years old were divided into two groups: $group_1$(Control group) include (40)healthy people and $group_2$ (40) Hyperthyroidism patients.The results showed that there was a significant elevate in the value of the Adiponectin hormone in $group_2$ compared to the control group.In contrast, it was observed that there was a decrease in the level of the Visfatin hormone in the $group_2$ compared with the control group, and as for lipid profile, it was noticed that there was a clear and significant decrease in all values of lipids in the $group_2$ compared to the control group.

The present study was carried out estimation of Visfatin and Adiponectin hormone in Hyperthyroidism patients, in addition to understand the relationship between Visfatin hormone and other related hormones T_3 and T_4, as so as the level of lipid profile.

Keyword
Visfatin Adiponectin, Lipid profile, Hyperthyroidism.

Introduction

Hyperthyroidism is an expression of hyperactive tissue in the thyroid gland, leading to excess production and therefor an excess of free circulating in thyroid hormones: T_4 and T_3 or both and TSH serum reduction[1].

Hyperthyroidism inhuman is characterized by multiple disturbancesinvolving significant energy spendingas well as excessive metabolic substratemobilization and utilization [2].

Adipose tissue is a very active endocrine organ secreting a variety of dissolvable productscalled ‘adipokines’ with both actions autocrine and paracrine. They have functions heat body control(thermogenesis), appetite control, reproductive functions and thyroid gland. All these soluble products may produces local and generalized inflammation, involving obesity-associated vascular diseasesinvolvingatherosclerosis,insulin resistance, hypertension, and diabetes.[3]

Thyroid hormones and adipokines have sharing somephysiological functions in common, such as organize of energy consumption, lipids and glucose metabolism[4,5], therefore it isbelievable, that there is a relationship between theadipose tissue effects and thyroid axis. Thyroid disorders may influence effects of adipose tissues, which contributes to other metabolic dysfunctions. In the same line with this, changes in lipolysis also present in thyroid dysfunction patients[6].

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Thyroid disordersis related with different metabolic disorders, due to thyroid hormones effects on main metabolic pathways. Thyroid hormones influence the basal energy expenditure by regulating the metabolism of protein, lipids and carbohydrates. This might be a direct role or an indirect role by modulation of other control hormones such as catecholaminesor insulin[7], alsohave been reported to alter secretion of adipokines such as Adiponectin,Leptin,Resistin andVisfatin.[3]Patients with Thyroid disorders typicallyexperiencevariation in appetite, thermogenesis and body weight. Alterations of lipolysis in fat tissue result secondary to alteration in the functional status ofthyroid gland. Hyperthyroidism is linked with weight loss inspite of increased appetite due to the increasing in metabolic rate and increasing gut motility. Decreasing in the levels of serum lipid as well as storage of lipidsis typical of hyperthyroid case.[8]

Adiponectin ADP is one of these adipokines,known asaPM_1, ACRP30,GBP28 andAdipoQ,has 244-amino acid protein include four differentiable domains and exists in five different configurations, which binds three types of receptors.[9]"Adiponectin"exerts multiple biological effects throughout the body mediated by the specific receptors AdipoR1, AdipoR2, and T-cadherin.[10]Adiponectin improves the oxidation of fatty acid and influence the sensitivity of insulin by increasing AMP-activated protein kinase phosphorylation and action in the muscle and liver. In addition, ADPlowering body fat by increasing catabolism of fat and energy outlay. These actionsincludecentraland peripheral mechanisms.[11]

Visfatin, an adipokinealso named as pre-B cell colony-enhancing factor (PBEF), 52-KDa protein is anextremelypreserved;existin living organisms from bacteria to human[12]. Visfatinwas isolated and identified as adipocytokine byFukuhara and his group in 2005 expressed at a much higher level in visceral than subcutaneous adipose tissue[13]. Visfatinis also named nicotinamide phosphoribosyltransferase (NAMPT) because of its effective and biochemical similarity with NAD biosynthesized from nicotinamide [14]. Fukuhara *et al.* [13] used the term "Visfatin" for this substancebecause its predominant releaseby visceral fat VAT. Visfatin is a highly enriched in the visceral fat of both humans and mice. Visfatinis also expressed in human and animal muscles and hepatocytes.[15]

Material and Methods

A total of 80 patients of both gender between 20- 60 years old were collected from Iraqi hospitals and privet laboratories in Mosul and Erbil governorate from the period 1/9/2020 to 1/2/2021. The diagnosis was dependent on the low concentration of thyroid-stimulating hormone (TSH) and the high concentration of thyroid hormones, andtheywere divided into two groups:
$Group_1$: Control group,include 40 patients have normal serum levels of thyroid hormones and do not have chronic disease.
$Group_2$: the hyperthyroidism,include (40) patients with high abnormal levels in their hormones.

Data have been taken from the patients, which contain personal information, symptoms and disease they may have.Blood samples have been collectedfor measuring Thyroid-stimulating hormone (TSH), Thyroxine(T_4), Triiodothyronine (T_3), Adiponectin,Visfatin and Lipid profile concentrations.

Collecting samples:(5) mlof veinous fasting blood had been collect, put in a tightly gel tube, left at room temperature for 20 minutes, then separated by a centrifuge at a speed of 3000

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rpmfor a period of 15 minutes to obtain the serum, then removed by a special micropipette and divided into several parts and placed in a dry and sterile plastic tube Eppendorfand finally frozen in a deep freezer at(- 20) ºC until the hormone and biochemical tests were estimated.

Hormonal tests:The concentration of the hormones TSH, T_4, T_3concentration were determined by using a prepared analysis kit manufactured by the French company Biomerieux, which depend on the Enzyme immunoassay competition method with final Fluorescent detection (ELIFA)

Adiponectin and Visfatin were be measured byprepared analysis kit manufactured by Sunlong and MybiosourceCompanyrespectively, which depend on the enzyme-linked immunosorbent assay(ELISA).

Biochemical tests

Lipid profiles(Total cholesterol TC, Triglycerides TG and HDL-c) were been measured via the Enzymatic method by using a prepared analysis kit manufactured by the French CompanyBiolaboSAS.

Serum level of LDL-cwas calculated byFriedewald formula[16], which was based on theassumption that VLDL-c is present in serum at aconcentration equal to 1/5 of Triglycerideconcentration.

$VLDL - C = \frac{TG}{5}$Therefore:

LDL-c = TC - [HDL-c + TG / 5]the formula is only valid when allconcentrations are given in (mg/dl), and at serumTriglyceride concentration of less than400mg/100ml.[17]

Statistical analysis

The data were analyzed according to the simple experiments system, using the complete random design and the Duncan multi-range test, the significant different parameters were distinguished by different alphabetic letters at a probability level of 1%. (SAS software) was used in the statistical analysis(SAS, 2004)[18].

Results

In Table 1, 2, the results showed a significant increaseat ($P \leq 0.01$) in T_4, T_3 and Adiponectin in Hyperthyroidism group compared with control group. In contrast showed a significant decreaseat ($P \leq 0.01$) in TSH, Visfatin, and all parameters of lipid profile in-group $_2$ compared with control group.

Table 1: Hormonal levels in Control and Hyperthyroidism patients

Groups / Parameters	Group$_1$ (no.=40)	Group $_2$(no.=40)
TSH µIU/ml	1.78 ± 0.70 a	0.84 ± 0.11b
T_4pmol/l	11.29 ± 2.29 b	31.44 ± 7.99 a
T_3pmol/l	4.20 ± 0.71 b	10.62 ± 3.51 a
ADP (ng/dl)	5.13 ± 0.94 b	5.92±1.51 a
Visfatin (ng/dl)	9.29 ± 1.90a	4.66 ± 0.876b

The no. followed by different letters means there is significant difference.

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The values is means ± standard deviation SD

Table 2: Lipid profile levels in Control and Hyperthyroidism patients

Groups / Parameters	Group$_1$ (no.=40)	Group $_2$ (no.=40)
TC (mg/dl)	130.35 ± 10.34a	116.59±15.17b
TG (mg/dl)	117.20 ± 14.82a	83.47± 17.03b
HDL (mg/dl)	48.27 ± 8.41 a	42.82± 6.92 b
LDL (mg/dl)	105.61 ± 12.33a	90.37±16.28b
VLDL (mg/dl)	23.29 ± 2.98a	16.61± 3.55b

The no. followed by different letters means there is significant difference.
The values is means ± standard deviation SD

Discussion

The results showed a significant increase of Adiponectin concentration in hyperthyroidism group with (5.92 ± 1.51) ng/dl compared to the control group with (5.13 ± 0.94) ng/dl. This is in line with the findings of the Yaturu*et al*.(2004)[19].The findings of studies of the relationship between hormones of thyroid gland and ADP in humans are contradictory. Till date, there have been few studies related to the alterationin release of ADP in thyroid dysfunction in human[3].Hyperthyroidism has been associated with increased levels of adiponectin, whereas hypothyroidism is not associated with significant alteration in adiponectin[20].ADP expression rises in tandem with an increase of thyroid hormones in rats with hyperthyroidism, whereas in hypothyroid rats the opposite occurs[21]. Cabanelas*et al*. (2010)[22]mentioned that in the subcutaneous adipose tissue T_3 was downregulated ADP mRNA expression , On the opposite direction T3 control was appeared to elevate the expression of ADP mRNA and its production by mouse brown adipocytes culture[23]. Seifiand his group (2013)[24]showed a reduce in mRNA values of adipoR1 and adipoR_2 result from administration of methimazole in adipose tissues of rats with hypothyroidism, whilst in hyperthyroid rats, it has been shown that mRNA values of ADP receptors were increased. In White adipose tissue, there is a positive relationship between the expression values of the gene for ADP receptor and the levels of thyroid hormones, indicating that thyroid hormones regulated ADP receptors gene expression are in hyperthyroidism and hypothyroidism.

Correlation between adiponectin and thyroidhormones is still unclear, in some studies Adiponectin levels have been found to be higher in hyperthyroidism whereas other studies show that levels of thyroid hormones remain unchanged in hyperthyroid.[25]

The results showed a significant decrease of Visfatin concentration in hyperthyroidism group with (4.66 ± 0.87) ng/dl compared to the control group with (9.29 ± 1.90) ng/dl.

A few studies have investigated the correlation between Visfatin and thyroid hormones. According to some experimental findings, T_3may accelerating he differentiation of adipocyte by increasing Visfatin levels[26], whilst the study of MacLaren*et al*. (2007)[27]that T_3 has been shown to reduce Visfatin mRNA expression in adipocytes type 3T3-L1.

Patients with hyperthyroidismtypically lose lean body mass, which is thought to be conjugated by reduce inVisfatin secretion. However, high levels ofVisfatinhave been reported

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in hyperthyroidism, whereas hypothyroid patient's levelswere observed to be decrease. This could be due to the compensatory rise in levels of Visfatinin response to hyperthyroidism's high metabolic rate, which accelerate fat breakdown[3].

Ozkaya*et al*. (2009)[28] studied the serum Visfatinvalue in patients with hypothyroidism, hyperthyroidism, in addition to healthy subjects before treatment and after it. Hyperthyroid patients had low level of Visfatin compared with the hypothyroid group and controls. Plasma Visfatinvaluereduced after treatment in the hypothyroid group, in the other hand it increased after treatment in the hyperthyroid group. A significant positive correlation between Visfatin and TSH levels and a significant negative correlation betweenVisfatin levels and T_3 and T_4 values were observed.Abdelsalam andEdrees (2015)[29]mentioned asimilar decreasing of serum Visfatin inhyperthyroid rats induced experimentally. Suchdiscrepancies between study results could beexplained by different patient characteristics, coexisting autoimmunity, and methodological agents.On the other hand, since TSH receptor is expressed in adipocytes, observed changes might result from TSH receptor stimulation in adipose tissue potentially leading to produce of Visfatin[30].

Our findings observed a significant decrease in all parameters of lipid profile in hyperthyroid patients ($group_2$) than control group in p value $P \leq 0.001$

Hormones from thyroid gland (THs)have variety effects on digestion, absorption, synthesis and catabolism of lipids[31]. THscontrols thecholesterolsynthesis across variety mechanisms. Liver consider being the major site for cholesterol biosynthesis. 3-Hydroxy-3-Methyl-Glutaryl Coenzyme A Reductase (HMGCR) is the determining enzyme in biosynthesis ofcholesterol thatis also controlled by numbers of hormones includingthyroid hormones,insulin,glucocorticoids, glucagon andestrogen[32].

Thyroid hormoneshavevital role in lipid metabolism regulation. They primarily regulate gene expression related to lipids metabolism via the nuclear receptors of hormonesα and β. Hyperthyroidism result in abnormalities of lipid profile. In last years, receptor β1-selective analogue of thyroid represents a new class of hypolipidemicsubstance have been developed. Some of these T_3 analogues are very strong in decreasing serum cholesterol and TG in animal models and human clinical researches[31]. Moreover, the activity of the enzymes which involved in lipoprotein metabolism and reverse cholesterol transport, like hepatic lipase (HL)[33], lipoprotein lipase (LPL)[34], CholesterylEsters Transfer Protein (CETP)[35], and Lecithin-Cholesterol Acyltransferase (LCAT)[36]are increased by THs.

Our study agrees with studies conducted by Nouh, *et al*. 2008, they found that hyperthyroidism is associated with decrease the level of total cholesterol, HDL-C.[37]

Gebhard*et al* (1992) agreement with our study theymentioned increased biliary elimination of cholesterol leads to decrease levels of plasma cholesterol in patients with hyperthyroidism[38].The cholesterol transformation into bile acids is necessary for the maintenance of cholesterol hemostasis in body. The enzyme for bile acid synthesis is under regulated by cholesterol 7-hydroxylase (CYP7A1), which is controlled by hormones ofthyroid gland[39].

It has been hypothesized that a highly clearance rate may result in lowering the levels of plasma cholesterol in hyperthyroid patients[38]. However, induce the 3- hydroxy-3-methylglutaryl-coenzyme A (HMGCoA) reductase, which is the first step in cholesterol

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biosynthesis controlled by thyroid hormones[40]. On the other hand, the LDL receptors areincreased resulting in low cholesterol concentration[41]. Thyroid hormones may affectmetabolism of HDL by raising the activity of cholesterol ester transfer protein (CETP), which exchanges cholesteryl esters from HDL2 to the very low-density lipoproteins (VLDL) and TGs to the opposite direction[42].

The both production and removal of plasma triglycerides regulated and controlled bythyroid hormones[43]. With respecting to fat metabolism increasing thyroid hormonelevels would be accelerate breaking down of triglycerides (TGs) that storage in the adipose tissue, which leads to concentration and transformation of non-esterified fatty acids (NEFA). This elevated of fatty acid availability is correlated with an increase in the rate of lipid oxidation [1].Also lipoprotein lipase (LPL) and the hepatic lipase (HL) stimulate by thyroid hormones, the first one is responsible for catabolizes (breakdown) the TG-rich lipoproteins, while the second one responsible for hydrolyzes HDL_2 to HDL_3 and subscribe to the conversion of intermediate-density lipoproteins (IDL) to LDL and in turn LDL to small dense LDL (sd LDL)[44,45].

In addition, T_3up-regulatethe apolipoprotein AV (ApoAV), that isplay a fundamental actionfor regulation of TG. Actually, higherApoAV levelswere related to decrease in TGs levels[46]. Suggested mechanisms for this impactinvolvereduction of hepatic VLDL-TG production and raisingin the levels and activity of plasma LPL, leading toraising of lipoprotein remnant creationdue to promote LPL-mediated lipolysis of VLDL-TG. Inaddition, Apo AV has been correlated to higher clearance of lipoprotein core remnants, due toelevate hepatic uptake due to an enhanced affinity for the receptor of LDL [47]. This couldelucidate the lower levelsof VLDL-C and TG in current study.

Thyroid hormonesinfluence bothlipolysis and lipogenesis. Thyroid hormones administrate Lipoprotein Lipase (LPL) as a key enzyme to remove Triglycerides (TG) from circulating chylomicrons and Very Low Density Lipoproteins (VLDL). LPL catalyzes TG into non-esterified fatty acid and transporting to adipose tissue where it re-esterified and storage as TG [48]. Additionally, THs affects the levels of TG involves angioprotein-like 3 (ANGPTL3), a potent LPL inhibitor. Over expression of ANGPTL3 in mice significantly promotes total cholesterol, non-esterified fatty acid and TG. No change or decrease has been shownin the levels of TG in hyperthyroid condition, partly, due to T_3 down regulate ANGPTL3 and catalyze PLP, resulting in hydrolysis TG. Thereafter, T_3-mediated LDLR activation dramatically elevates clearing ability for LDL[49]. Thyroid hormone impacts TG homeostasis, which is also,includes regulating gene transcription of APOA5. Apolipoprotein A-V (ApoA5) is connected to HDL, VLDL and chylomicrons. ApoA5 controls TG valueby LPL-mediated TG hydrolysis and suppressing the formation hepatic VLDL-TG[31].

Conclusion

From our study, we can conclude that there is a positive relationship between Adiponectin and thyroid hormones in addition to negative relationship betweenVisfatin and thyroid hormones with decrease lipid profile.

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