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THE ROLE OF ADIPOKINES : LEPTIN, RESISTIN AND CRP IN THYROID DYSFUNCTION

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ABSTRACT : Hypothyroid happens when thyroid gland is underactive. This can exist at any age, but the risk raises as you become older, and it is most generally promoted via genetics. Hyperthyroidism is basically the reverse of hypothyroid. It happens when thyroid gland is hyperactive, making too much thyroid hormone. These hormones regulate the body's energy balance and have effects on adipokine level. There are several reports suggesting interrelation between adipokines (resistin and leptin) with thyroid dysfunction. This study was instituted to examine the influence of thyroid hormones in hypothyroidism and hyperthyroidism states on the levels of some adipokines, leptin, resistin and CRP in comparison with control group. Also, to study the correlation of serum leptin. Resistin and CRP with thyroid hormones in various disorders of thyroid gland. The present study included 35 Iraqismale patients for each state (hypothyroidism and hyperthyroidism) with age ranged between (18-68) years and 20 healthy controls with age ranged between (18-68)years. Serum samples were collected from National Diabetes Center which follows to Al- Mustansiria University in Baghdad from July 2018 to September 2018. Thyroid hormones (TSH, T_4 and T_3) were determined by using the ELFA technique.Detection of leptin and resistin levels in the serum were determined by an enzyme linked immunosorbent assay (ELISA) kits. Determination of C-Reactive Protein (CRP) by using I chromá device. The results showed that serum leptin levels in hypothyroid patientswere significantlyhigher than in control group($P \leq 0.01$), while serum leptin levels in hyperthyroid patients were not significantwith control group ($P \leq 0.01$). Also, observed significant findings in resistin levels were higher in hyperthyroid patients than hypothyroid patients and control group, while resistin level in hypothyroid patients was significant little high than control group ($P \leq 0.05$). There were non-significant negative correlations between T_3 and T_4 and leptin; also, non-significant positive correlations between TSH and leptin in hypothyroid patients. Whereas, there were significant negative correlations between T_3 and T_4 and leptin; also, significant positive correlations between TSH and leptin in hyperthyroid patients. There were non-significant negative correlations between T_3, T_4 and TSH with resistin level in hypothyroid patients and there were non-significant positive correlations between T_3 and T_4 and resistin; non-significant negative correlations between TSH and resistin in hyperthyroid patients. As well as, CRP levels were significantly higher in hypothyroid and hyperthyroid patients than control group ($P \geq 0.05$), on the other hand there was statistically significant difference between hypothyroid and hyperthyroid patients, CRP in hypothyroid patients were higher than hyperthyroid patients. However, we observed high-significant positive correlations between resistin and CRP with leptin levels in hypothyroid patients. The present study shows that there is complex relationship between adipokines(leptin, resistin and CRP) with thyroid hormones. They affect each other in their physiological function in the human body. Also we observe tight relationship between CRP and resistin with leptin.

Key words : Hypothyroidism, hyperthyroidism, leptin, resistin, CRP.

INTRODUCTION

Hypothyroid happens when thyroid gland is underactive. This can exist at any age, but the risk raises as you become older and it is most generallypromoted by genetics. Hyperthyroidism is basically the reverse of hypothyroid. It happens when thyroid gland is hyperactive, making too much thyroid hormone. THs play important roles in, growth, differentiation, and metabolism. THs : is required for normal function :of all tissues, with main effects on metabolic rate and oxygen consumption. Thyroid functions are controlled via the thyroid-stimulating hormone TSH (also called thyrotropin) of anterior pituitary (Marsili *et al*, 2013). Secretion of, this hormone is in turn increased, through thyrotropin-releasing hormone TRH: isalso dependent to negativefeedback control via high :circulating levelsof THs acting on anterior pituitary and hypothalamus. Adipocyte; is an active cell and not a store

Abbreviations: THs, thyroid hormones; TSH, thyroid-stimulating hormone; TRH, thyrotropin-releasing hormone; Tg, thyroglobulin; AT, Adipose tissue; IL, interleukin; TNFá, tumor necrosis factor-á; BAT, brown adipose tissue; WAT, white adipose tissue; CRP, C-Reactive Protein; FRTL-5 cells, Follicular rat thyroid cell line; cAMP, Cyclic adenosine monophosphate; ELFA, Enzyme Linked Fluorescent Assay; ELISA, enzyme linked immunosorbent assay; ANOVA, Analysis OfVariance; Rcorrelation coefficient; P, probability; SD, standard deviation.

of, excess energy. Fat cells produce several biologically active substances with different physiological functions. Adipose tissue AT expresses receptors, for of these substances (Martinez *et al*, 2015). These molecules, noun as adipocytokines or adipokines, may impact the function, as well as the structural integrity of other tissues. Adipocytokines have endocrine, autocrine and paracrine effects on the brain, skeletal muscles and liver (Jaleel *et al*, 2013). They take control feeding, immunity, thermogenesis, reproductive and thyroid hormones and neuroendocrine functions. Some instance s of these adipokines, are tumor necrosis factor-a (TNF-α), interleukin-18 (IL-18), leptin, ometin, resistin, adiponectin and visfatin. Adipocyte dysfunction as happens in obesity and in lipodystrophy can convert adipocytokine releasing from adipose tissue giving raise to metabolic and energy disorders (Hutcheson, 2015). In contrast, all those disorders which affect thyroid functions can also act in energy metabolism. Patients with, thyroid dysfunction, generally displays changes in the body thermogenesis, weight and lipolysis in AT (Martinez *et al*, 2015). Hypothyroid isassociated with a simple weight gain, reduce thermogenesis and metabolic rate. In contrast, hyperthyroid is linked with weight loss in spite of, increased appetite and, highmetabolic rate. As many ofthese changes are correlated with alterations in the function of AT (Al-Suhaimi, Shehzad, 2013). It seems of interest, estimating the relationship between adipokines, THs and thyroid dysfunction.,

Adipose tissue

Adipose tissue is a complex, essential and highly active metabolic and endocrine organ. Besides adipocytes, adipose tissue contains connective tissue matrix, nerve tissue, cells, endothelial cells, vascular smooth muscle cells, fibroblasts and immune cells such as macrophages and lymphocytes, together these components function as an integrated unit (Azamar *et al*, 2017). Adipocytes have large globules droplets of stored fat (triglycerides) which may be used for energy. These cells bulge or shrink based on whether fat is becoming stored or use (Rebiger *et al*, 2016). When muscles and other tissues needed energy, certain hormones bind to adipose cells and trigger the hydrolysis of triacylglycerol, resulting in the release of energy-rich fatty acids and glycerol a process known as lipolysis, the enzyme responsible for hydrolysis is lipase, which occurs in the blood, gastrointestinal juice, and adipose tissue (Berry and Rodeheffer, 2013). Adipose tissue not only responds to afferent signals from traditional hormone systems and the central nervous system but also expresses and secretes factors with important endocrine functions. These factors called adipocytokines or adipokines, which act at both the local (autocrine / paracrine) and systemic endocrine 64. Fat stored in adipose tissue derives from dietary fats or is generated in body. The term of AT a metabolically dynamic organ mentions to brown adipose tissue BAT and white adipose tissue WAT (Rebiger *et al*, 2016). BAT is found at birth and almost doesn't occur in adults, its role is linked with thermogenesis (heat production). In thebody, the plurality of adipose tissue includes WAT having adipocytes as well as others such as macrophages, fibroblasts, lymphocytes, endothelial cells and vascular smooth muscle cells (Wu, 2016). The sources of adipocytes may be bone marrow, lungs and blood vessels adventitia. There are also beige adipose is genetically different from both BAT and WAT, but burns calories to liberate energy such as BAT. Brown and beige fat cells acquire their color from the abundance of blood vessels and existence of iron-containing mitochondria over the tissue. Beige adipose tissue can also be generated from white adipose cells WAT (Wu *et al*, 2013). Adipose tissue AT is found in various sites in body, several of these locations involve the subcutaneous layer under the skin, around the heart,kidneys,nerve tissue,in yellow bone marrow, breast tissue, within the buttocks, thighsand abdominal cavity (Aguirre, 2014).

Classification of Adipokines according to functional role

Adipokines are protein mediators that secreted through adipocytes, peripheral blood mononuclear cells, macrophages, endothelial cells also bronchial, and alveolar epithelial cells. The total number of adipokines, both certified and supposed, is now more than fifty (Berry and Rodeheffer, 2013).

Growth and angiogenic factors : Fibroblast growth factors (FGFs), insulin-like growth factor-1 (IGF-1), nerve growth factor (NGF), hepatocyte growth factor (HGF), transforming growth factor-β (TGFβ), vascular endothelial cell growth factor (VEGF), angiopoietin-1; angiopoietin-2 andtissue factor (TF, coagulation factor 3).

Cytokines : (IL-1â),(IL-4),(IL-6), (IL-8), (IL-10), (IL-18), (TNFá), macrophage migration inhibitory factor (MIF), Complement-like factors, adipsinandadiponectin.

Adhesion molecules and Extracellular Matrix ECM components : Vascular cell adhesion molecule-1 (VCAM-1), α2-macroglobulin, intercellular adhesion molecule-1 (ICAM-1), collagen types I, III, IV, and VI, fibronectin, matrix metalloproteinase 1 (MMP1), MMP7, MMP9, MMP10, MMP11, MMP14 and MMP15.

Acute phase proteins : C-reactive protein (CRP), plasminogen activator inhibitor-1 (PAI-1), serum amyloid A3 (SAA3) andhaptoglobin(Brennan and Mantzoros, 2006).

Chemokines : Chemerin; monocyte chemotactic protein-1 (MCP-1), macrophage inhibitory protein-1 alpha (MIP-1α), normally T cell expressed and secreted (RANTES) and regulated upon activation (Coffey *et al*, 2015).

Metabolic processes : Adipocyte fatty acid binding protein (FABP4), apolipoprotein E (apoE),retinol binding protein-4 (RBP4), omentin; resistin, vaspin, apelin, visfatin and leptin (Derosa *et al*, 2013).

Leptin

Leptin is derived from the Greek word "leptos", that means thin. Leptin was the primary recognized adipokine, its primary structure is consist of 167 amino acids and it is firstly expressed in adipose tissue AT (Coffey *et al*, 2015). Leptin works immediately on leptin receptorsin cell membraneof various types of cells in humans body specially, and in vertebratescommonly (Rebiger *et al*, 2016). The major site of action leptin is the hypothalamus that is a part of the central nervous system CNS. Non-hypothalamic targets of leptin arementioned to as peripheral targets (Stern *et al*, 2016). The first function of leptin is regulation of adipose tissuemass by hypothalamus intermediate effects on hunger,food energy use, physical practice and energy balance (Linkov *et al*, 2014). Out of the brain, in the periphery of body, secondary functions of liptin arealteration between fetal and maternal metabolism; modification of energy expenditure an elective factor in puberty activator of immune cells, activator of beta cells, and growth factor (Kumor *et al*, 2013). A big amount of leptin is secreted via subcutaneous adipocytes than through the visceral adipocytes, but is commonly synthesized and secreted by gastric chief cells in stomach (Boelen *et al*, 2012). Its existence has also been found in many other tissues, involving mammary glands, the placenta, breast milk, ovaries, testes, stomach, hypothalamus and pituitary gland. Circulating levels of liptin are directly proportional to the body fat mass. These levels range from (5-10) ng/ml in healthy persons to (40-100) ng/ml in obese persons (Al-Shoumer *et al*, 2018). A temporary increase happens during a meal, while leptin levels reduce with fasting, leading to a profound changes in hormone levels and energy balance (Yildiz *et al*, 2017).

Resistin

Resistin is another distinct adipocyte derived signaling cysteine rich molecule made up of 114 amino acids and was founded at first in obese mice, it has been noted that circulating resistin levels are raised in obese humans (Eke *et al*, 2013). Human resistin has been founded in tissues such as placenta, skeletal muscle, small intestine, thymus, stomach, spleen, thyroid gland and uterus (Beaven *et al*, 2013). Resistin expression was maximal in WAT than in BAT. Resistin is expressed in adipose tissue AT at a less level, but is mainly expressed in macrophages. Resistin is named in order to its resistance to the action of insulin (Alman *et al*, 2017). It is considered a pro-inflammatory molecule that also plays a serious role in the pathogenesis of diabetes. The release of resistin is often promoted by the inflammatory process, IL-6, hyperglycemia, hormones like growth hormone (GH) and gonadal hormones (Aksoy *et al*, 2013).

C-Reactive Protein (CRP)

C-reactive protein is a homopentameric acute-phase inflammatory protein, named native CRP (nCRP), is characterized via a dislike arranging of five conforming non-covalently bound subunits (Slevin *et al*, 2015). These five subunits lie in similar direction around a centric pore and set in a distinctive with a two-layered beta sheet, which raises up to 1,000 fold at locations of inflammation and infection (Thiele *et al*, 2014). A highly conserved plasma protein that was initially discovered in 1930 by Tillet and Francis while investigating the serum of patients suffering from the acute stage of Pneumococcus infection and was noun for its reaction with the capsular C-polysaccharide of Pneumococcus (Derosa *et al*, 2013). CRP is produced firstly inthe liver hepatocytes, but also by smooth muscle cells, macrophages,lymphocytes, endothelial cells and adipocytes (Braig *et al*, 2017). There is presently increasing evidence that CRP plays significant roles in inflammatory processes and host responses to infection involving the apoptosis, phagocytosis and the production of cytokines, specially IL-6, IL-10 and TNF-á (Nicola and Jason, 2018). Transcriptional inducement of CRP gene commonly occurs in hepatocytes in liver in response to increase levels of inflammatory cytokines, particularly IL-6 (Krayem *et al*, 2017). CRP amounts reduce greatly over 18–20 hours, nearby to the half-life of CRP. CRP plasma levels raise from around 1 μg per mL to over 500 μg per mL in (24–72) hours of acute tissue such as ruin trauma and gradual cancer (Ansar and Ghosh, 2013). IL-6 is reported to be major inducer of CRP gene expression, with IL-1 improving the effect (Czarnywojtek *et al*, 2014). However, in spite of IL-6 is needful for CRP gene induction, it isn't enough to realize this alone. There are many factors which may change CRP levels involvingage; gender; smoking; weight, lipid levels and blood pressure

(Seven *et al*, 2015).

MATERIALS AND METHODS

This was a cross sectional study which was conductedin National Diabetes Center which follows to Al-Mustansiria University in Baghdad from July 2018 to September 2018. The study included (70) men patients, 35 of them have hyperthyroidism and 35 have hypothyroidism, their ages between (18-68 years) old. As well as choosing random group included 20 sample of healthy men of ages between (18-68 years) old (Table 1). Thyroid hormones (TSH, T_4 and T_3) were determined by using the ELFA technique (Enzyme Linked Fluorescent Assay). Detection of leptin and resistin levels in the serum were determined by an enzyme linked immunosorbent assay (ELISA) kits.

Table 1 : Demographic distribution of study population.

Groups	No. of Individuals	Age (years)
Control	20	18 - 68 years old
Hypothyroidism	35	
Hyperthyroidism	35	

Statistical analysis

The statistical analysis was carried out by using statistical program (Minitab) and comparison between groups which were made by using one-way analysis of variance (ANOVA) and tried out the arithmetic means for parameters by using test of Duncan multiple ranges to delimitating significantly different especially between groups. Pearson correlation coefficient (R) between T_3 and other parameters was reported by using regression plots. The level of statistical significance was taken at ($P \leq 0.01$) and ($P \leq 0.05$).

RESULTS

The results of this study revealed that the mean ± SD of T_3, T_4 and TSH levels for hypothyroidism patients respectively were (0.712 ± 0.0288) ng/ml, (3.359 ± 0.743) µg/dl and (26.36± 1.712) µUI/ml.While mean ± SD ofT3, T4 and TSH levels for hyperthyroidism patients respectively were (2.978 ± 0.494) ng/ml, (16.151 ± 3.141) µg/dl and (0.049 ± 0.019) µUI/ml. The mean ± SD of T_3, T_4 and TSH levels for control group respectively were (1.615 ± 0.308) ng/ml, (8.556 ± 2.076) µg/dl and (2.230 ± 0.107) µUI/ml, as shown in Table 2 and Figs. 1, 2, 3 respectively.

The mean ± SD ofLeptin levels for hypothyroidism patients, hyperthyroidism patients and control group respectively were (199.40 ± 17.1) pg/ml, (154.95 ± 16.86) pg/ml and (164.69 ± 10.02pg/ml), as shown in Table 2 and Fig. 4.

Previous studies investigating the associations between thyroid functions and adipocytokines are conflicting due to different patient characteristics, autoimmunity and probably nutritional condition. These current results agreed with Chen *et al* (2016), Singla *et al* (2016), Al-Hindawi (2018) found that serum leptin in hyperthyroid patients was not-significant withcontrol group. While serum leptin in hypothyroid patients was significantly higher than in control group (p= 0.001). However, the current results are incompatible with results for Nakamura *et al* (2000) and Diekman *et al* (1998) indicate that serum leptin is increased in subjects with hyperthyroidism. On the other hand, Yaturu *et al* (2004) indicated that serum levels of leptin did not change with change in the thyroid functional status.

The results of Pearson's correlation demonstrated in Tables 2, 3 and Figs. 7, 10, observe that there is negative correlation between leptin level with T_3 and T_4 levels; which confirmed current result of increase leptin level in hypothyroidism patients compared with control group and lower leptin level in hyperthyroidism patients than hypothyroidism patients.

The mean ± SD of Resistin levels for hypothyroidism patients, hyperthyroidism patients and control group respectively were (3.828 ± 0.145) ng/ml, (4.325 ± 1.031) ng/ml and (2.963 ± 0.383 ng/ml), as shown in Table 2 and Fig. 5.

In this study, significant findings in resistin levels were higher in patients group than control group (p= 0.044). These current results are compatible with results for Hedayati *et al* (2014), Yaturu *et al* (2004), Al-Hindawi (2018), Chen *et al* (2016). However, the current results are incompatible with results for Ceren *et al* (2013) and Iglesias *et al* (2003). They found that resistin level in hypothyroid patients was higher than hyperthyroid patients and control group.The results of Pearson's correlation demonstrated in Tables 2, 3 and Figs. 12, 8 observe that there is positive correlation (in hyperthyroid patients) between resistin level with T_3; which confirmed current result of raise resistin level in hyperthyroidism patients. Whereas there is negative correlation (in hypothyroid patients) between resistinwith T_3 hormone level and we found high significant positive correlation between resistin level withleptin level (Fig. 14), which may be current result of low increase inresistin level in hypothyroidism patients when compared with control group.

The mean ± SD of CRP levels for hypothyroidism patients, hyperthyroidism patients and control group respectively were (7.019 ±1.68) mg/L, (5.73 ± 1.82) mg/L and (2.754 ± 0.126) mg/L as shown in Table 2 and Fig. 6.

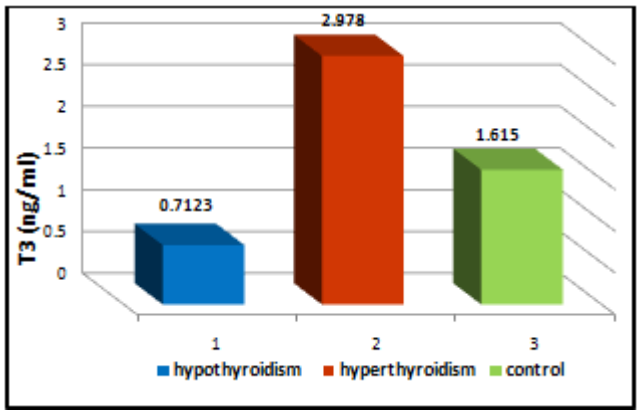

Fig. 1 : Levels of T_3 ng/ml in patients groups and control group.

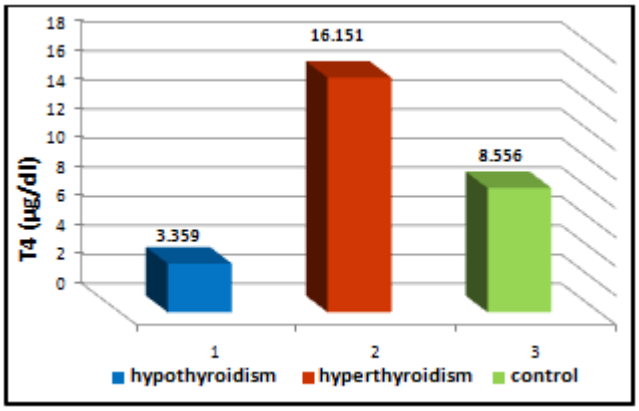

Fig. 2 : Levels of T_4 µg/dl in patients groups and control group.

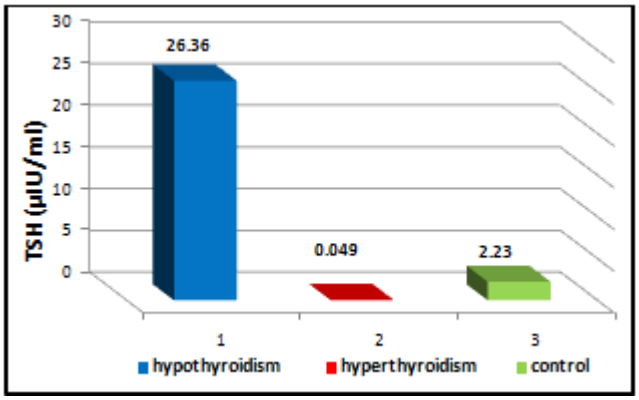

Fig. 3 : Levels of TSH µUI/dl in patients groups and control group.

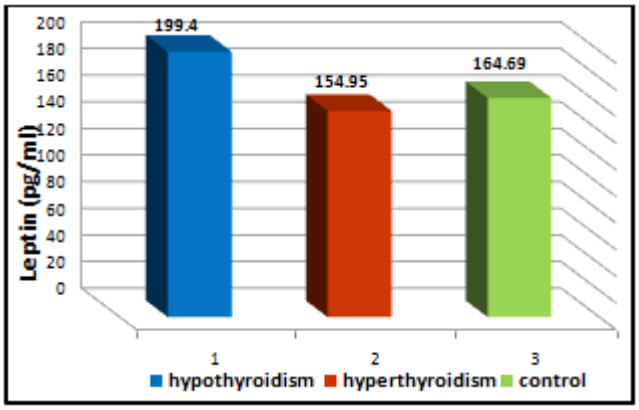

Fig. 4 : Levels of Leptin in patients groups and control group.

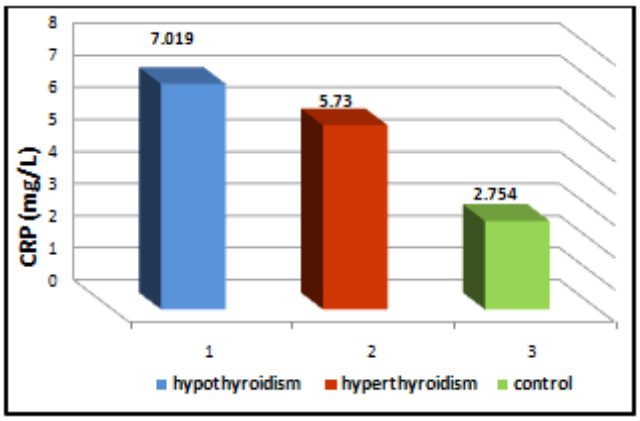

Fig. 5 : Levels of Resistin in patients groups and control group.

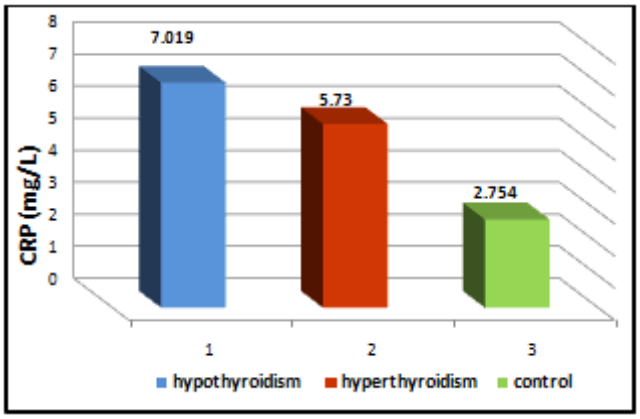

Fig. 6 : Levels of CRP in patients groups and control group.

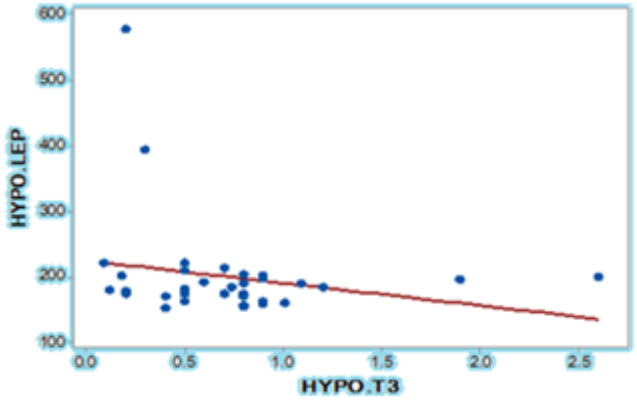

Fig. 7 : Correlation between T_3 with leptin in hypothyroid patients.

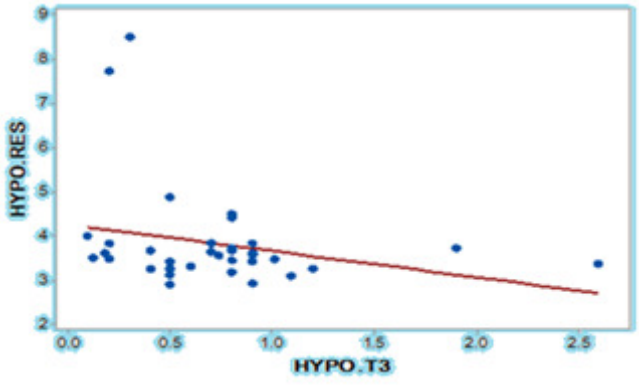

Fig. 8 : Correlation between T_3 with resistin in hypothyroid patients.

Table 2 : Arithmetic average for Thyroid hormones and Adipokines Concentrations in the studied group.

Group	Meam ± SD					
No.	T3 (ng/ml)	T4 (µg/ dl)	TSH (µIU/ml)	Leptin (pg/ml)	Resistin (ng/ml)	CRP (mg/L)
Control 20	1.615 ± 0.308b	8.556±2.076b	2.230 ± 0.107b	164.69 ± 10.02b	2.963± 0.383c	0.126± 2.754c
Hypothyroid 35	0.712 ±0.028c	3.359 ± 0.743c	1.712 ± 26.36a	199.40 ± 17.1a	3.828 ± 0.145b	1.68± 7.019a
Hyperthyroid 35	2.978 ± 0.494a	16.151 ± 3.14a	0.019 ±0.049c	154.95 ± 16.86b	4.325 ± 1.031a	5.73 ± 1.82b
P-value	0.0008	0.00006	0.0009	0.001	0.044	0.092

The similar letters mean that there are no significant differences between groups and the different letters mean that there are significant differences between them. Ages for all groups between (18- 68) years old.

Table 3 : Correlation coefficient (R) between thyroid hormones with parameters in hypothyroid patients.

Parameters	Statistical variables	T3	T4	TSH	Leptin	Resistin
T4	R	0.750	—	—	—	—
	P	0.000**	—	—	—	—
TSH	R	-0.350	-0.391	—	—	—
	P	0.043*	0.022*	—	—	—
Leptin	R	-0.216	-0.061	0.088	—	—
	P	0.213ns	0.729ns	0.620 ns	—	—
Resistin	R	-0.254	-0.136	-0.078	0.821	—
	P	0.140ns	0.436ns	0.660 ns	0.000**	—
CRP	R	-0.083	0.193	-0.110	0.748	0.452
	P	0.634ns	0.267ns	0.535 ns	0.000**	0.000**

R: Correlation coefficient, **P:** p-value, * P<0.05, ** P<0.01, **ns :** Not significant.

Table 4 : Correlation coefficient (R) between thyroid hormones with parameters in hyperthyroid patients.

Parameters	Statistical variables	T3	T4	TSH	Leptin	Resistin
T4	R	0.808	—	—	—	—
	P	0.000**	—	—	—	—
TSH	R	-0.210	-0.221	—	—	—
	P	0.225ns	0.202ns	—	—	—
Leptin	R	-0.699	-0.738	0.347	—	—
	P	0.000**	0.000**	0.041*	—	—
Resistin	R	0.050	0.031	-0.017	0.099	—
	P	0.774ns	0.857ns	0.922ns	0.573ns	—
CRP	R	-0.091	-0.084	0.008	0.272	-0.084
	P	0.603ns	0.631ns	0.962ns	0.114ns	0.631ns

R: Correlation coefficient; **P:** p-value;* P<0.05;** P<0.01; **ns** :Not significant.

CRP levels were significantly higher in patients group than control group (P = 0.092), on the other hand there was statistically significant difference between hypothyroid and hyperthyroid patients, CRP in hypothyroid patients was higher than hyperthyroid patients. These current results are compatible with results for Czarnywojtek *et al* (2014), Kamel *et al* (2018). However, the current results are incompatible with results for Jouda *et al* (2019) and Savas *et al* (2016). They found CRP level was significant higherin hyperthyroidism than hypothyroidism and control, while nodifferences between hypothyroidism and control. The conflicts between these findings and the results put up above may have various causes, involving sample volume, age and sex.

The results of Pearson's correlation demonstrated in Tables 2, 3 and Figs 9, 13 observe that there is negative correlation (in hypothyroid patients) between CRP level with T_3 hormone; highsignificant positive correlation between CRP level with leptin Fig. 11 and resistin levels respectively; which may be current result of increase in CRP level in hypothyroidism patients more than hyperthyroidism patients and control group, whereas there is negative correlation between CRP level with T_3 and T_4 hormones respectively; which confirmed current result of relative height in CRP level in hyperthyroidism patients more than control group. In present study, we note that leptin has a clear impact on CRP level.

DISCUSSION

The present study is designed to study the adipocyte hormones namely leptin, resistin, and CRP levels in relation to thyroid functional status. Our results clearly show that THs play a major role in the leptin,resistin and CRP levels. As we have noticed that there is an effect between them like the clear impact of leptin on resistin and CRP levels incase of lack of thyroid hormones (hypothyroid).

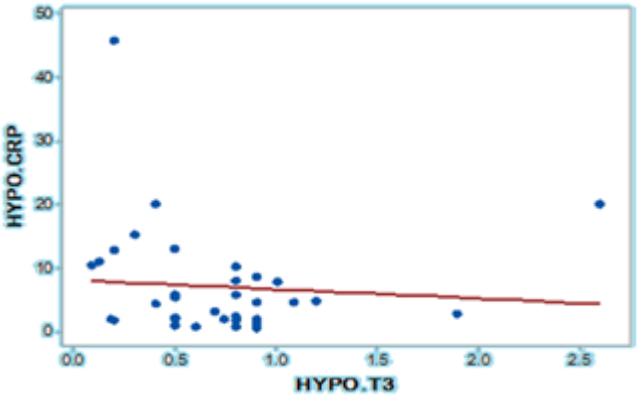

Fig. 9 : Correlation between T_3 with CRPin hypothyroid patients.

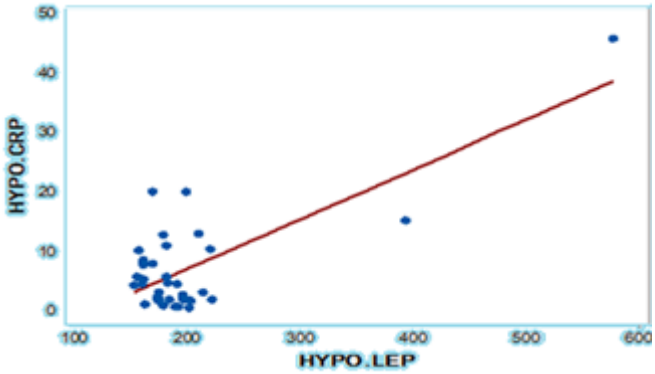

Fig. 10 : Correlation between Leptin with CRP in hypothyroid patients.

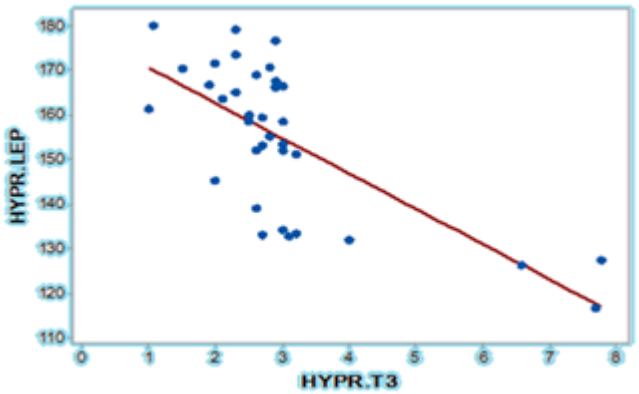

Fig. 11 : Correlation between T_3 with leptin in hyperthyroid patients.

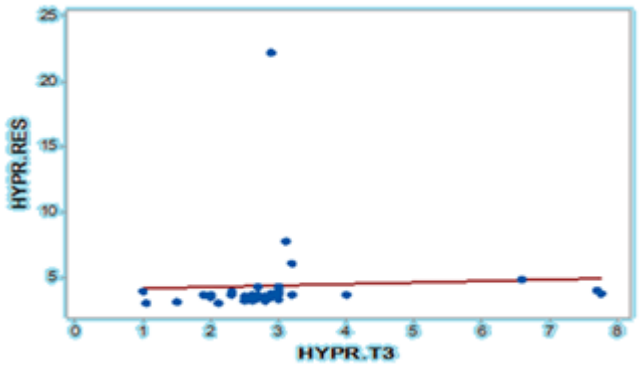

Fig. 12 : Correlation between T_3 with resistinin hyperthyroid patients.

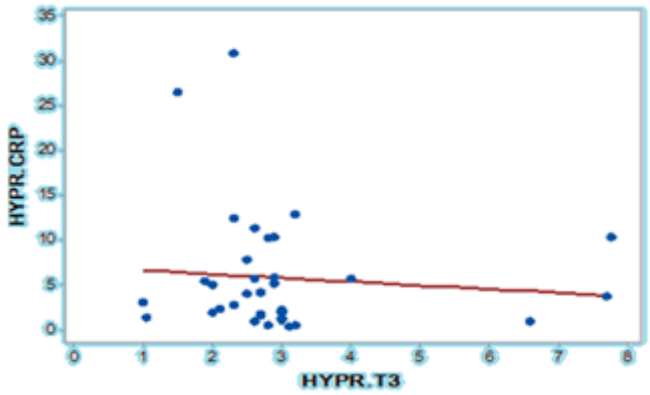

Fig. 13 : Correlation between T3 with CRP in hyperthyroid patients.

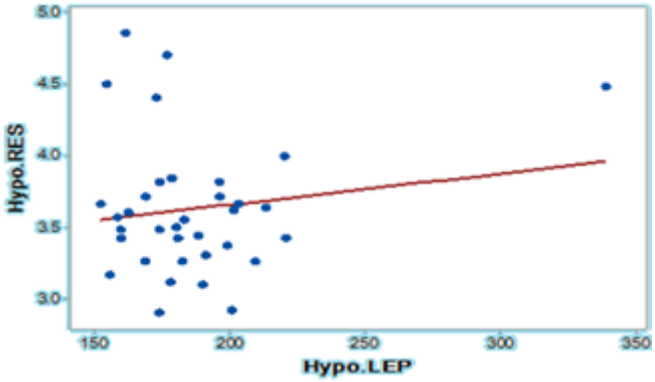

Fig. 14 : Correlation between resistin with liptin in hyperthyroid patients.

The adipocytokines serve as causative or protective factors in the development of disorders in the states of thyroid dysfunction. Abnormal levels of adipocytokinesin hypo- and hyperthyroidism have been reported with controversial results (Cinar and Alper, 2013). Leptin, a polypeptide hormone, which is produced by adipocytes in suitability to their triglyceride TG content, associates alterations in body energy (fat) stores to adaptive responses in the principal control of energy equilibrium through binding to and stimulating the long form of its receptor (LEPR-B) in brain (Prevot *et al*, 2018). Leptin has been considered to do its weight-reducing action not only by promoting hypophagia (reduced food intake), but also by increasing energy expenditure/thermogenesis. Leptin has been found to become a main regulator of body weight and metabolism. These findings in a chain of physiologic responses which cause the body to burn fat instead of continue to store overflow (Kaiyala *et al*, 2015). Leptin controls central and peripheral iodothyronine deiodinase action and conversion of T_4 to T_3, as well as, increases D2 action centrally and cause an raise of T_3 (Seven, 2001). T_3 inhibited leptin in a dose-dependent way, an impact also seen in the existence of norepinephrine. The raise in leptin secretion was introduced by an increase in leptin mRNA expression

(Zimmermann *et al*, 2003). On other side, *in vivo* and *in vitro* rat studies recognizedthat raise serum T_3 leads to a lack in leptin mRNA expression at white adipose tissue WAT and serum leptin levels (Medina *et al*, 2004). On the other side, leptin has a stimulatory impact on the liberation of TSH (Ortiga *et al*, 2002). Also, there is suggestion include the presence of direct stimulatory influence of leptin on T_4 released from thyroid gland (Parimisetty *et al*, 2016).

Thyroid hormones and leptin influence each other and can regulate body composition and metabolism by compound mechanisms (Al-Hindawi, 2018). Reduction of change in leptin levels with thyroid functional status possibly reflects to change in fat mass between hyperthyroid and hypothyroid objects (Corbetta *et al*, 1997). Other examinations have been achieved *in vitro* through studies of cultured cells, the advantage of that is dealing with a pure cellular system without involvement from fasting, feedback regulations and other factors. The disadvantage is that the studies aren't do in the intact organism with all the other physiological regulating effects. Leptin's impact has been studied both in a cell line and in thyrocytes of human via various investigators andexamining different end-points. In follicular rat thyroid cell line FRTL-5 cells, leptin preventediodide uptake induced by TSH, also, TSH- cAMP-induced sodium iodide symporter (NIS) and thyroglobulin mRNA expressions. In a human cell system, leptin prevented TSH stimulated cAMP and Tg release from primary cultures of natural human thyrocytes. However, because leptin would normally promote TRH as a result of that thyroid hormones production. It is not very easy to clarify why leptin should prevent thyroid cellular function, except if it should be an uncertain cytokine effect inhibited for some pathophysiologic situations or an unknown feedback mechanism (Zimmermann *et al*, 2003).

Hypothyroidism and diabetes are two most general medical conditions correlated with increased levels of leptin and with other case called leptin resistance; the failure of increased leptin levels to repress feeding and mediate weight loss in general patterns of obesity. Resistance of leptin oriented hyperleptinaemia is a general trouble in obese individuals in association with hypercholesterolaemia (Zhou, 2013). It is a reduced response to leptin, even if there is adequate of it circulating over the body. This resistance is based on an incorrect message that the body is hungry and thus, multiple hormonal mechanisms are stimulated to raise fat stores, as the body attempts to reverse the realized state of starvation. Even with a mild caloric intake, this is supposed to raise the risk of weight gain or obesity. These mechanisms may be in part caused by a down regulation ofleptin receptors (LEPR-B), which happens after a prolonged exposure to excessive leptin levels 2. Leptin comes in cerebrospinal fluid (CSF) in proportion to leptin levels, but absorption is lower in peoples with the elevated plasma leptin concentrations. So, it is possible that there is a saturable CSF-leptin transfer leads to an visibleleptin resistance between obese individuals with elevated plasma leptin concentrations (Chmielewski *et al*, 2019). It was supposed that regulation of leptin transmit across the blood–brain barrier might be defective in individuals with elevated plasma leptin levels. As well as, elevated plasma leptin concentrations in obese men are correlated with little resting energy expenditure (REE) (Abreu *et al*, 2015).

Panayoula *et al* (2013) emphasized this study suggestion when they supposed that the expression of resistin, IL-6, TNF-á and IL-1â from human mononuclear cells, could be promoted by hyperleptinemia and hyperinsulinemia and possibly by diabetes and atherosclerosis. Here, we note that the effect of T_3 on the increase level of resistin was more effective than leptinlevel. Our results clearly show that the thyroid hormones (especially T_3 hormone) play a major role in the resistin levels (Panayoula *et al*, 2013). Other report on 76 patients and 30 controls evidenced that resistin levels are similar in hyperthyroidism patients and controls (Sieminska *et al*, 2008). As well as other report showed that resistin concentrations in the control group were similar to hypothyroidism group and so thyroid hormones THs and resistin had not relationship (Guldiken *et al*, 2008). Few information on the influences of weight loss on the regulation of resistin levels is accomplished. New studies have shown that energy restriction and weight reduction has no correlated with alterations in resistin levels in healthy subjects with normal weight (Nogueiras *et al*, 2003). In spite of adipocytes express increase levels of TSH receptors that function comparable to those in thyroid, indicating that TSH contributes in the regulation of adipocyte functions involving secreting adipocytokines like resistin and leptin. Researches investigating thyroid disorders and their consequences on adipocytokine profiles are restricted and results are so variable and opposite (Roef *et al*, 2012). In present study observed that leptin has a clear impact on CRP level. Increased CRP level in thyroid disorders was reported in past studies.

In a cross-section whole study CRP levels were found to be raised in patients with hypothyroidism (Kvetny *et al*, 2004). The mechanization of CRP raising in hypothyroid is unknown. Some of signs and symptoms in hypothyroidism patients suppose an anomaly of

inflammation. These idea may be result of an interaction of IL-6 on TNF and IL-1, this interaction outcome from the elevated CRP in hypothyroidism. Other fundamental mechanisms of CRP raised in both hyperthyroidism and hypothyroidism stay unclear. Except for the mentioned earlier cytokines, reduction of thyroid hormones THs cause for slowing down all metabolic rate, and each biochemical processes may be ruined under those conditions. So, the rate of CRP removal may lead to CRP serum level excess. In conflict, hyperthyroidism leads to quick metabolic activity, thatmay result in the hyperactivity of adrenergic nervous system (sympathomimetic), promotion of immune system and greatly raised peripheral blood flow, every those circumstances might lead to an increase of CRP concentration (Lombardi *et al*, 2015).

Marta *et al* (2014) showed high plasma levels of leptin and C-reactive protein (CRP) in many conditions, involving obesity, cardiovascular risk. It is interesting, these two biomarkers seem to be capable to regulate their bioavailability, by complex mechanisms which haven't been quite cleared yet. They abstract also molecular studies observing that leptin is capable to stimulate CRP production from endothelial cells and hepatocytes *in vitro* and powwow the studies addressing the potential that *in vivo* leptin management may be capable to modify serum CRP levels. Moreover, they discuss two studies showing that CRP immediately links leptin in extra-cellular settings so, reducing its biological actions. As well as, they reported genetic proofthat general alterations in leptin receptor spots are correlated with CRP blood levels (Marta *et al*, 2014).

Finally, there is a relationship between leptin and thyroid gland perhaps through an impact of leptin on negative feedback of thyroid hormones THs, also effect on thermogenesis. Updatingleptin troubles and reducing weight will improve thyroid functions. But surely a big study group is needed to explain this relationship. There is relationship between resistin and thyroid through T_3 raise mRNA expression and there is an potent relationship between cytokines and resistin levels in hypothyroid state. TSH has a direct impact on leptin secretion by promoting TSH-receptor on adipocytes. New researches supply evidence for a correlation between serum levels of TSH and leptin in men with euthyroid state and in obese subjects, respectively. There are several studies examining circulating leptin levels in thyroid dysfunctions. Yet, the results are so polemic. Results of this study supposes that serum resistin and leptinis probable to be consider as a substantiation extra test for the diagnosis of thyroid disorders involving hypothyroidism and hyperthyroidism in patients likely. So, the measurement of resistin and leptin, may be prohibit the false diagnosis of thyroid evaluation.Most ofthyroid disorders are induced by inflammation, and CRP have a tendency to be raised in acute and chronic inflammatory cases. Its secretion is elevated in response to a cytokines complex network,specially IL-6, IL-1 and tumor necrosis factor-a TNF-α. Based on Marta *et al* (2014) studies and these current findings, can prove the relationship between the levels of leptin and CRP in thyroid dysfunction commonly. Leptin is a significant source of circulating inflammatory cytokines, like IL-6, that in turn stimulate CRP synthesis. In parallel, leptin itselfis capable to directly promote CRP synthesis from liver and from the blood vessels. Significant variations in CRP levels for thyroid disorders patients observed in present study emphasize that inflammation has an important essential role on pathogenesis of thyroid dysfunctions in any case of their thyroid dysfunction kind. Also, the current study observedthat the CRP is a useful biomarker for hypothyroidism patients. Totally, the data reviewed show that the increase of CRP observed in hypothyroid individuals may raise leptin resistance, participating to the pathogenesis of thyroid disease, and show up a potential connect between conditions, like leptin resistance and hypothyroidism which may be responsive to pharmacologic treat attacked to the of disturbance leptin-CRP interaction.

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