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### RESEARCH ARTICLE

#### STUDY OF ASSOCIATION OF RESISTIN AND LEPTIN WITH THYROID HORMONES IN HYPOTHYROID PATIENTS

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##### Key words:-

Resistin, Leptin, Hypothyroidism

#### Abstract

**Objective:** The present study was aimed to evaluate the levels of resistin and leptin in hypothyroid patients and to find a possible association of thyroid hormones with resistin and leptin.

**Material and Methods:** The present study was conducted on 100 previously diagnosed hypothyroid (PDH) patients (38 Males & 62 Females) and 100 newly diagnosed hypothyroid (NDH) patients (44 Males & 56 Females) attending the outpatient clinics or admitted in wards of J.L.N. Hospitals, Ajmer. 100 healthy control subjects of same age group of either gender were selected for the study. Blood samples were drawn from patients and controls, after overnight fast of at least 8 hours. Estimation of Serum Leptin, Resistin, free T<sub>3</sub>, free T<sub>4</sub>, and TSH was done by using Enzyme- Linked Immunosorbant Assay (ELISA) technique. Differences in the parameters among the groups were analyzed by ANOVA test followed by its Tukey HSD post hoc analysis. Correlations between variables were tested using the Pearson rho (r: Correlation coefficient) correlation test.

**Results:** Findings of the present study shows that the levels of serum fT<sub>3</sub> (1.79 ± 0.29 pg/mL) and serum fT<sub>4</sub> (0.34 ± 0.11 ng/dL) were significantly lower in NDH group compared to PDH group (fT<sub>3</sub> = 3.00 ± 0.32 pg/mL & fT<sub>4</sub> = 0.81 ± 0.15 ng/dL) and control group (fT<sub>3</sub> = 3.12 ± 0.31 pg/mL & fT<sub>4</sub> = 0.85 ± 0.11 ng/dL) whereas serum TSH levels were significantly higher in NDH group (40.59 ± 13.55 µIU/mL) compared to PDH group (5.34 ± 1.47 µIU/mL) and control group (3.23 ± 1.04 µIU/mL) [Table 1; Figure 1]. Serum leptin levels were significantly higher in NDH group (21.37 ± 6.44 ng/mL) compared to PDH group (16.51 ± 4.47 ng/mL) and control group (11.15 ± 5.29 ng/mL) [Table 2]. A highly significant variation (p<0.0001) in the levels of serum leptin was found between the groups. Serum resistin levels were significantly higher in NDH group (14.50 ± 2.72 ng/mL) compared to PDH group (11.33 ± 1.59 ng/mL) and control group (7.78 ± 1.19 ng/mL) [Table 2]. Highly Significant difference (p<0.0001) in resistin levels was found between the groups.

**Conclusion:** It was suggested that thyroid dysfunction does not affect the leptin levels and also thyroid hormones were not involved in the synthesis and secretion of leptin. Further studies are required to gain more insight into the relationship between leptin and thyroid

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dysfunction. Resistin shows a significant correlation with thyroid hormones which indicate that serum resistin might be considered as a confirmation extra test for the early detection of atherosclerosis and atherosclerosis induced conditions in hypothyroid patients.

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## Introduction:-

Hypothyroidism is considered as one of the most common endocrine disorders in India as well as throughout the world. Hypothyroidism shows diverse clinical manifestations which include lethargy, cold intolerance, weight gain, fatigue, menstrual irregularities etc<sup>19</sup>. Earlier, energy storage is considered as the main function of adipose tissue but further studies have recognized adipose tissue as the largest endocrine organ which secretes a variety of hormones known as adipokines or adipocytokines. These adipokines shows their effect on reproductive hormones, thermogenesis, neuroendocrine function, food intake and immunity<sup>9</sup>. Discovery of obese gene and leptin proves to be a milestone and provides a new perspective towards adipose tissue.

Leptin is also known as satiety hormone which is secreted by adipose tissue and considered as an important factor in the regulation of food intake and energy storage<sup>20</sup>. In circulation leptin occurs in both free and bound forms and concentration of serum leptin is directly proportional to the amount of body fat present. Both alterations in the levels of leptin and thyroid dysfunction are associated with noticeable changes in energy expenditure and body weight therefore it is important to understand the association between them and to study their mutual interactions<sup>16</sup>.

Resistin is a polypeptide which contains 108-amino acids and is mostly produced in adipose tissue, macrophages, muscle and pancreas. It is believed that resistin might have a role in the regulation of obesity and insulin resistance<sup>6</sup>. Resistin, as a pro-inflammatory cytokine, is also believed to be associated with inflammatory diseases independent from insulin resistance<sup>10</sup>. On the basis of various studies done recently, researchers are now considering that resistin might have some role in thyroid function. The exact relationship between resistin levels and thyroid functions has not been established yet.

## Material and Methods:-

### Subjects:

The present study was conducted on 100 previously diagnosed hypothyroid (PDH) patients (38 Males & 62 Females) and 100 newly diagnosed hypothyroid (NDH) patients (44 Males & 56 Females) attending the outpatient clinics or admitted in wards of Medicine Department, J.L.N. Hospital, Ajmer. 100 healthy control subjects of same age group of either gender were selected for the study. Patients with diabetes mellitus, chronic renal failure, congestive heart failure, pregnant women and smokers were excluded from the study.

### Sample collection and Measurement:

Blood samples were drawn from patients and controls, after overnight fast of at least 8 hours. Five ml blood was collected in plain vial (without any anticoagulant) and was allowed to clot for 30 minutes at room temperature and then centrifuged at 3000 rotations per minute (rpm) for 10 minutes to obtain clear non-haemolysed serum (Haemolysed serum samples were excluded from analysis). Estimation of Serum Leptin, Resistin, free T<sub>3</sub>, free T<sub>4</sub>, and TSH was done by using Enzyme- Linked Immunosorbant Assay (ELISA) technique.

### Statistical Analysis:

Variables were presented as Mean  $\pm$  Standard deviation (S.D.). Differences in the parameters among the groups were analyzed by ANOVA test followed by its Tukey HSD post hoc analysis. Correlations between variables were tested using the Pearson rho (r: Correlation coefficient) correlation test. The accepted level of significance for all statistical analyses used in the study was  $P \leq 0.05$  (two tailed P value).

## Results:-

Findings of the present study shows that the levels of serum fT<sub>3</sub> ( $1.79 \pm 0.29$  pg/mL) and serum fT<sub>4</sub> ( $0.34 \pm 0.11$  ng/dL) were significantly lower in NDH group compared to PDH group (fT<sub>3</sub> =  $3.00 \pm 0.32$  pg/mL & fT<sub>4</sub> =  $0.81 \pm 0.15$  ng/dL) and control group (fT<sub>3</sub> =  $3.12 \pm 0.31$  pg/mL & fT<sub>4</sub> =  $0.85 \pm 0.11$  ng/dL) whereas serum TSH levels were

significantly higher in NDH group ( $40.59 \pm 13.55$   $\mu\text{IU/mL}$ ) compared to PDH group ( $5.34 \pm 1.47$   $\mu\text{IU/mL}$ ) and control group ( $3.23 \pm 1.04$   $\mu\text{IU/mL}$ ) [Table 1; Figure 1].

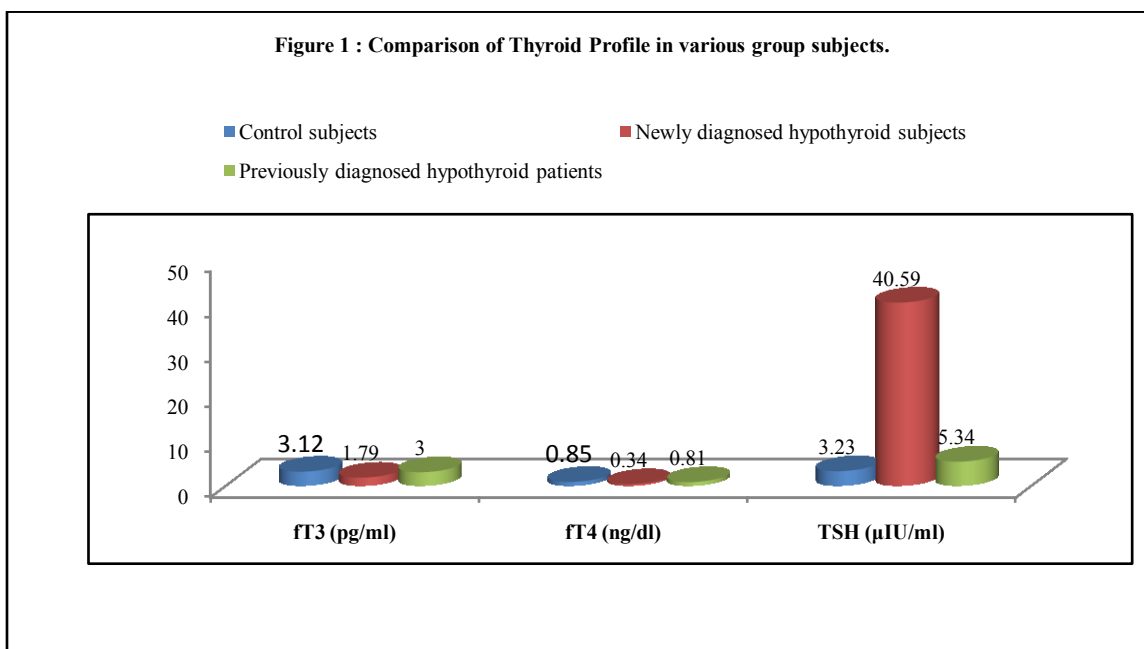
**Table No.1:-** General and Biochemical parameters.

S.No.	Parameter	Control group [Mean $\pm$ S.D.]	NDH group [Mean $\pm$ S.D.]	PDH group [Mean $\pm$ S.D.]
1	Age (Years)	$40.41 \pm 5.81$	$43.89 \pm 5.30$	$46.04 \pm 5.71$
2	BMI ( $\text{Kg/m}^2$ )	$23.88 \pm 1.54$	$26.84 \pm 1.41$	$24.45 \pm 1.01$
3	fT <sub>3</sub> (pg/mL)	$3.12 \pm 0.31$	$1.79 \pm 0.29$	$3.00 \pm 0.32$
4	fT <sub>4</sub> (ng/dL)	$0.85 \pm 0.11$	$0.34 \pm 0.11$	$0.81 \pm 0.15$
5	TSH ( $\mu\text{IU/mL}$ )	$3.23 \pm 1.04$	$40.59 \pm 13.55$	$5.34 \pm 1.47$

Serum leptin levels were significantly higher in NDH group ( $21.37 \pm 6.44$  ng/mL) compared to PDH group ( $16.51 \pm 4.47$  ng/mL) and control group ( $11.15 \pm 5.29$  ng/mL) [Table 2]. A highly significant variation ( $p < 0.0001$ ) in the levels of serum leptin was found between the groups.

Serum resistin levels were significantly higher in NDH group ( $14.50 \pm 2.72$  ng/mL) compared to PDH group ( $11.33 \pm 1.59$  ng/mL) and control group ( $7.78 \pm 1.19$  ng/mL) [Table 2]. Highly Significant difference ( $p < 0.0001$ ) in resistin levels was found between the groups.

In the present study a non significant correlation of leptin with S.fT<sub>3</sub>, S.fT<sub>4</sub> and TSH was found both in NDH and PDH group whereas BMI shows a significant positive correlation with leptin in NDH group in comparison to a non significant correlation in PDH group [Table 3; Figure 4,5].



**Table No. 2:-**

S.No.	Parameter	Control group [Mean $\pm$ S.D.]	NDH group [Mean $\pm$ S.D.]	PDH group [Mean $\pm$ S.D.]
1	Resistin (ng/mL)	$7.78 \pm 1.19$	$14.50 \pm 2.72$	$11.33 \pm 1.59$
2	Leptin (ng/mL)	$11.15 \pm 5.29$	$21.37 \pm 6.44$	$16.51 \pm 4.47$

**Table No. 3:-** Correlation of S. Leptin with various variables (fT<sub>3</sub>, fT<sub>4</sub>, TSH and BMI) in PDH group and NDH group.

Parameter	r value		p value		Significance	
	PDH	NDH	PDH	NDH	PDH	NDH group

	group	group	group	group	group	
fT <sub>3</sub>	-0.049	-0.171	0.628	0.088	NS	NS
fT <sub>4</sub>	-0.045	-0.073	0.656	0.470	NS	NS
TSH	0.033	0.165	0.744	0.100	NS	NS
BMI	0.096	0.237	0.342	0.017	NS	S

S – Significant

NS – Non-Significant

Resistin shows a strong negative correlation with S.fT<sub>3</sub> in NDH group in comparison to a weak negative correlation in PDH group. A significant negative correlation of resistin with S.fT<sub>4</sub> was found in NDH group in comparison to a non significant correlation in PDH group. A highly significant positive correlation of resistin with TSH was found in NDH group in comparison to non significant correlation in PDH group. A non significant correlation of resistin with BMI was found both in NDH and PDH group [Table 4; Figure 2,3].

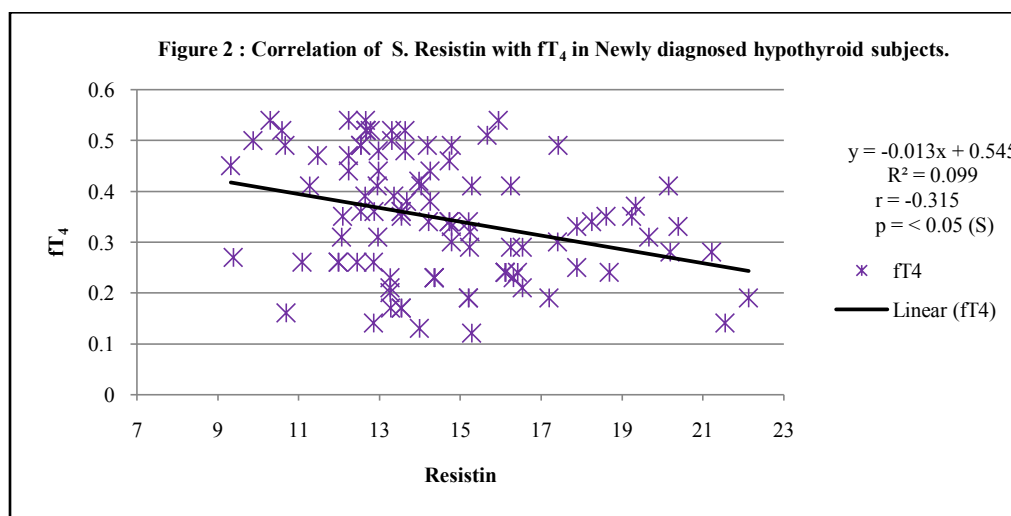
**Table No.4:-** Correlation of S. Resistin with various variables (fT<sub>3</sub>, fT<sub>4</sub>, TSH and BMI) in PDH group and NDH group.

Parameter	r value		p value		Significance	
	PDH group	NDH group	PDH group	NDH group	PDH group	NDH group
fT <sub>3</sub>	-0.282	-0.557	0.004	<0.001	S	HS
fT <sub>4</sub>	-0.116	-0.315	0.250	0.001	NS	S
TSH	0.132	0.454	0.190	< 0.001	NS	HS
BMI	0.099	-0.019	0.327	0.851	NS	NS

S – Significant

NS – Non-Significant

HS – Highly Significant

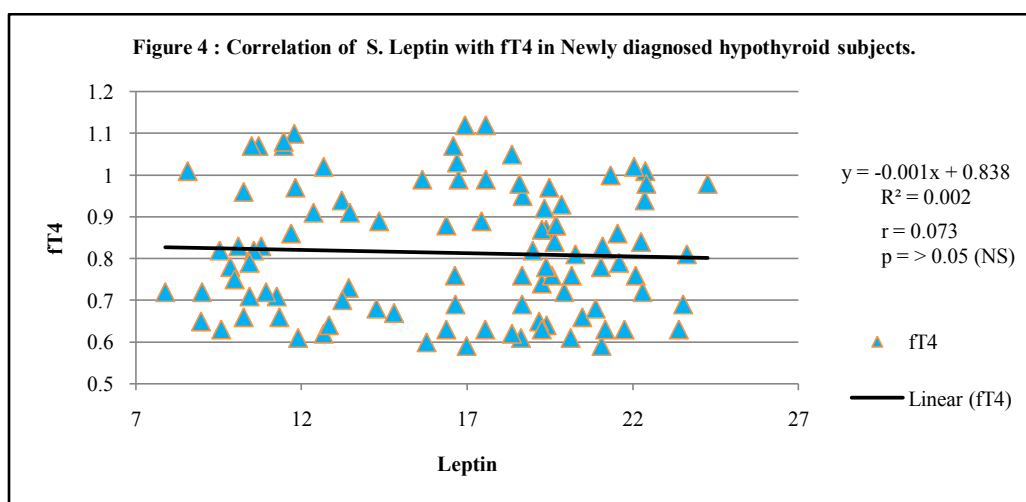
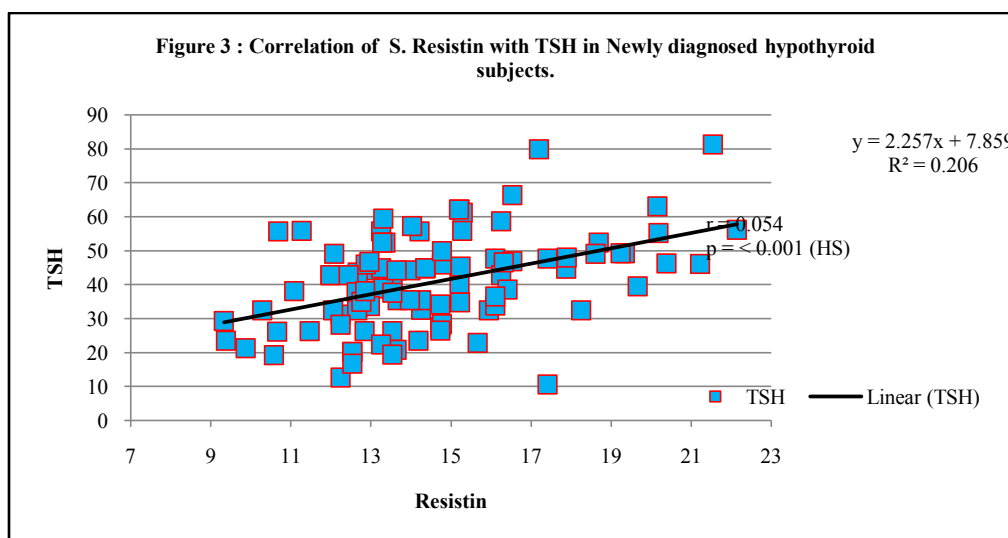


### Discussion:-

Hypothyroidism is a common endocrinological problem which plays a significant role in metabolic and development processes worldwide as well as in India. Hypothyroidism is a common disorder and because of its nonspecific clinical presentation, it remains under-diagnosed. As compared to the general population, patients with hypothyroidism show a greater propensity for co-morbidities and complications. We observed that hypothyroidism was more prevalent in women than men.

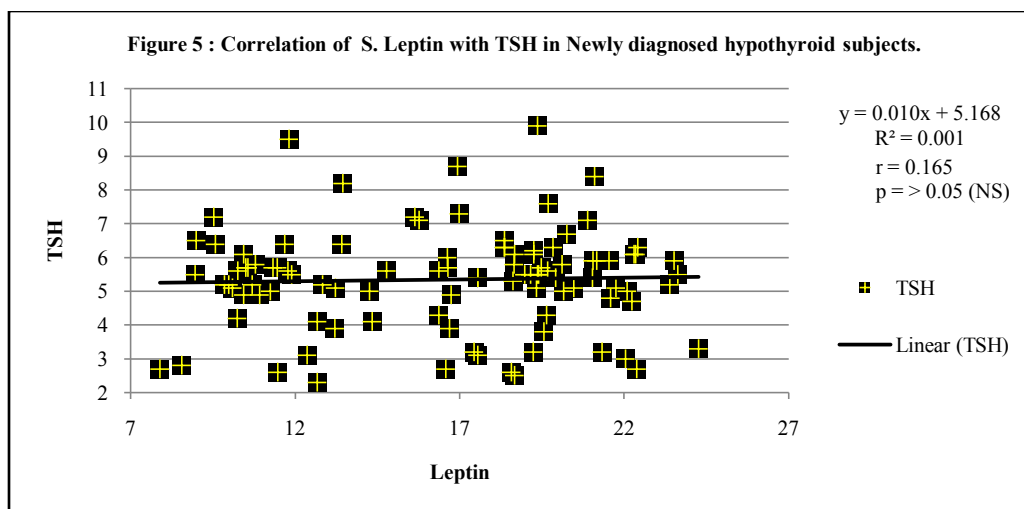
In the beginning, leptin was considered as a hormone which is intended to prevent obesity but after various studies it was now recognized that leptin also controls the switch from the fed to the starved state which represents a significant interaction between leptin and thyroid hormones. In our study a non significant correlation of S.Leptin with S.fT<sub>3</sub>, S.fT<sub>4</sub> and S.TSH was found both in NDH and PDH group. BMI shows a significant positive correlation with S.Leptin in NDH group in comparison to a non significant correlation in PDH group. Findings of our study is in agreement with other studies conducted by Sreenan et al. 1997, Ozata et al. 1998, Kautzky-Willer et al. 1999,

Yaturu et al. 2004, Santini et al. 2004 which reported that thyroid dysfunction does not affect the leptin levels and also suggested that thyroid hormones were not involved in the synthesis and secretion of leptin.



Leptin not only shows its effect on energy consumption and appetite but also helps in the conversion of  $T_4$  to  $T_3$  by regulating the activity of central and peripheral iodothyronine deiodinase<sup>12</sup>. In hypothyroidism increase in the levels of serum leptin is probably due to the reduced effect of thyroid hormones on leptin receptor and adipocytes. Findings of our study is in agreement with other studies which reported that thyroid dysfunction does not affect the leptin levels and also suggested that thyroid hormones were not involved in the synthesis and secretion of leptin<sup>13</sup>. A recently published study on females with higher levels of serum leptin reported that sex hormones are involved in the regulation of leptin synthesis. Another possible explanation of these sex based differences in leptin concentration is due to differences in the body composition<sup>14</sup>.

Resistin is a proinflammatory cytokine which is supposed to play a significant role in the development of insulin resistance and obesity. Synthesis and secretion of resistin as a polypeptide mainly occurs in adipose tissue, macrophages, pancreas and muscles. Resistin is also associated with various inflammatory diseases other than insulin resistance and plays a significant role in energy homeostasis. The relationship between resistin levels and thyroid disorders is not very clear.



In the present study S.Resistin shows a strong negative correlation with S.ft<sub>3</sub> in NDH group in comparison to a weak negative correlation in PDH group. A significant negative correlation of S.Resistin with S.ft<sub>4</sub> was found in NDH group in comparison to a non significant correlation in PDH group. A highly significant positive correlation of S.Resistin with S.TSH was found in NDH group in comparison to non significant correlation in PDH group. A non significant correlation of S.Resistin with BMI was found both in NDH and PDH group. The relationship between resistin levels and thyroid disorders is not clear. Yaturu et al. (2004) found a positive correlation between thyroid hormones and resistin levels whereas Iglesias et al. (2003) did not found any change in the resistin levels of euthyroid and hypothyroid subjects. Ziora et al. (2011) in their study conducted on anorexia nervosa patients reported a positive positive correlation between ft<sub>4</sub> and serum resistin levels. Kalpan et al. (2012) compared euthyroid subjects with thyroidectomy induced hypothyroid subjects and found no significant change in the levels of adiponectin, leptin and resistin. The possible reason behind this conflicting data on thyroid status and resistin levels is the interaction of other adipokines with resistin.

Resistin, as a pro-inflammatory cytokine, is also believed to be associated with inflammatory diseases independent from insulin resistance. Role of resistin as an inducer of insulin resistance has been reported as the focus of investigations in the studies so far<sup>8</sup>. However, the fact that expression of resistin also occurs in bone marrow cells, specifically in macrophages and leucocytes and the presence of molecules of the RELM family in inflamed tissues indicates that resistin might have some role in the process of inflammation<sup>7</sup>. The exact relationship between resistin levels and thyroid functions has not been established yet. Increase in the levels of serum resistin may result in a chronic sub inflammatory state which plays a significant role in the development of insulin resistance, type II diabetes and CVD.

### Conclusion:-

Thyroid hormones and thyroid stimulating hormone controls the regulation of a broad spectra of metabolic parameters. Leptin shows its effect on energy expenditure possibly due to the mediation of thyroid hormones but further studies regarding the role of thyroid hormones on leptin are still required to gain more insight into the relationship between leptin and thyroid dysfunction. S. Resistin shows a significant correlation with thyroid hormones which indicate that serum resistin might be considered as a confirmation extra test for the early detection of atherosclerosis and atherosclerosis induced conditions in hypothyroid patients.

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