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Alteration and Prognostic Value of Serum Adipocytokines and Growth Factors in Patients with Hyperthyroidism

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Abstract

Objective: The current study aims to find predictive significance of diagnosis hyperthyroidism by evaluating the adipocytokines (Apelin and lipocalin-2) and growth factors (FGF-21 and VEGF) in the blood serum of groups under study.

Methodology: Fifty-five individuals participated in this study and were classified into two groups. The first group (G1) consisted of (35) patients of hyperthyroidism (20 females and 15 males), the second group (G2) consisted of (25) subjects which represented the control group, the age range of under study groups were (18–76) years. The measurement of serum adipocytokines and growth factors was conducted using quantitative sandwich enzyme linked immune sorbent assay (ELISA).

Results: The results show that hyperthyroid patients have significantly higher levels of serum Apelin, lipocalin-2, FGF-21 and VEGF levels as compared to control group. The ROC curves analysis showed that the sensitivity of Apelin, Lipocalin-2, FGF-21, and VEGF as biomarkers for hyperthyroidism were79%, 94%, 72%, and 81%, respectively, with specificities of 96%, 92%, 91%, and 84, respectively.

Conclusions: According to the findings of this study, hyperthyroidism causes an increase in adipocytokines (Apelin and lipocalin-2) and growth factors (FGF-21 and VEGF) in the blood, altered levels of adipocytokines and growth factors may contribute in the diagnosis of Hyperthyroidism.

Keywords: Hyperthyroidism, adipocytokines, growth factors

Introduction

Hyperthyroidism is delineated as the excess secretion and release of thyroid hormone by the thyroid gland sequencing in improperly high serum levels. Hyperthyroidism can influence multiple organ systems, involving the cardiovascular, nervous, gastrointestinal, and hepatic systems. The consummate ubiquitous form of hyperthyroidism is caused by escalated thyroid hormone secretion in Graves' disease, and the others are toxic multinodular goiter and solitary toxic adenoma.[1] Common symptoms of hyperthyroidism include losing of weight despite increased appetite, restlessness, tremors, weakness in the muscles, and heat sensitivity.[2]

Thyroid hormones (THs) control the body's energy equilibrium and affect the levels of adipocytokines.[3,4] TSH receptors are present in adipose tissues, suggesting their involvement in the regulation of adipocytokines that control energy balance.[5]

Adipokines are biologically active molecules released by adipose tissue that have a wide-ranging impact on health and disease. Adipokines are cytokines produced not only in white adipose tissue but also in the fat surrounding the pancreas, and they play a role in the body's inflammatory response.[6]

Apelin is a peptide that serves as a ligand of the APJ receptor. Its therapeutic abilities might be favorable for insulin resistance treatment, although in cancer exerts unfavorable effects, by stimulating the tumor growth. Apelin exhibits an impact on exocrine secretion of pancreas, as well as anti-inflammatory activities.[7]

Lipocalin 2 (LCN2), also known as Neutrophil Gelatinase-Associated Lipocalin (NGAL), is a widely expressed protein that has been found to exert many different functions. It has been suggested that is has a role in the regulation of energy metabolism also.[8] Any change in the thyroid function with alteration in Role of Changes in Some Adipokines with Obesity in Relation to Thyroid Function thyroid profile can affect the metabolic functions that finally disturb appetite, body weight, and adipose tissue and can also contribute in the pathogenesis of obesity, this interrelation that observed among thyroid function and adipokines production may contribute to the metabolic consequences of thyroid diseases.[9,10]

Growth factors play a crucial role in regulating a broad variety of biological processes and are regarded as powerful therapeutic agents in tissue engineering and regenerative medicine in the past decades.[11] Fibroblast growth factor 21 (FGF21) is a member of the FGF super family, and endogenic FGF21 is predominantly released from hepatocytes.[12] FGF21 has been considered as an important endogenous regulator for glucose-lipid metabolism.[13,14] Both administration and transgenic overexpression of FGF21 protect animal models from diet-induced obesity and metabolic disorders.[15]

Vascular endothelial growth factor (VEGF) plays a crucial role in angiogenesis; it binds to a particular VEGF receptor (VEGFR) to activate the growth, survival and proliferation of vascular endothelial cells.[16]

The aim of this study was to evaluate levels of Adipocytokines and Growth factors in sera of patients with hyperthyroidism, and to explore the diagnostic accuracy of Adipocytokines and Growth factors as a predictor of hyperthyroidism in Iraqi population.

Methods and Materials

Patients and Study Design

The current study was conducted at Golan General Hospital in Akre which started from September 2024 to December 2024, the study samples included (35) individuals with hyperthyroidism (20 females and 15 males), and (25) healthy individuals who do not suffer from thyroid diseases or any other diseases, and the ages of the study samples ranged between

(18–76) years. This study was approved by the Ethics Committee of Salahaddin University (28B,2024). Ethical approval statements were acquired for all participated individuals, depending upon Helsinki Declaration of World Medical Association. The exclusion criteria included; subjects with tumor, sepsis, severe injury, diabetes mellitus, hypertension, acute and chronic renal disease, coronary artery disease, peripheral artery disease, neurological disease or any other chronic disease or malignancy.

Sample Collection

Blood samples (5 mL) were collected in gel tubes and allowed to clot for 20–30 minutes. Serum was then separated by centrifugation at 4000 rpm for 10 minutes. Hormonal test and TSH were immediately measured in a portion of the serum by Cobas. The remaining serum was stored at –20°C for subsequent analysis of Lipocalin2, IGF-1 and FGF-21 using ELISA kits from Sunlong Company.

Sample Size

The sample size needed for the study was calculated by a power analysis using the G-Power software, and it showed 98% power when a minimum sample of 35 subjects were included in the study.

Laboratory Assessments

The following serum levels were measured:

VEGF **levels** by using Sandwich-ELISA kit (catalog No.: Catalogue Number: QS0051Fe) Validity Period: six months
Lipocalin2 **levels** by using Sandwich-ELISA kit (catalog No.: Catalogue Number: EL0252Hu) Validity Period: Two Years
IGF-1 **levels** by using Sandwich-ELISA kit (catalog No.: Catalogue Number: EL0235Hu) Validity Period: Two Years
FGF-21 **levels** by using Sandwich-ELISA kit (catalog No.: Catalogue Number: EL0216Hu) Validity Period: Two Years

Assay Principle

In this technique, antibody was coated on the microtiter well. A sample containing antigen was added to the well and allowed to react with the antibody attached to the well, forming antigen-antibody complex. After the well was washed, a second enzyme-linked antibody specific for a different epitope on the antigen was added and allowed to react with the bound antigen. Then after unbound secondary antibody was removed by washing. Finally substrate was added to the plate which was hydrolyzed by enzyme to form colored products.

Statistical Analysis

Statistical analysis was performed with (GraphPad9.0) statistical software. Results are expressed as means ± SE. The patient and control groups were compared by using Student-t test. The Chi-Square test was used for nominal variables. One-sample Kolmogorov-Smirnov test was used to assess the normality of data. Between groups comparisons of continuous variables were performed by independent sample t-test. Paired t-test was used for before and after intervention comparisons. Operating Characteristics of the Receiver "ROC" curve technique was applied to determine of any parameter as a diagnostic or marker tool for disease and the capacity to establish the "cut-off value" which of the best sensitivity and specificity. $P < 0.05$ was considered statistically significant.

Results

Table 1 presents the baseline characteristics of the study participants, including age and TSH levels. The mean age of participants was comparable across the groups: 42.30 ± 2.86 years in the control group and 40.86 ± 2.17 years in the hyperthyroidism group. TSH levels, however, varied significantly. The control group exhibited a mean TSH level of 1.716 ± 0.1701 IU/mL, which falls within the normal range. In contrast, the hyperthyroidism group had significantly lower TSH levels (0.02020 ± 0.003928 IU/mL), reflecting the characteristic suppression of TSH production by the elevated thyroid hormones in this condition. These findings highlight the distinct biochemical profiles associated with thyroid dysfunction, with the significant differences in TSH levels serving as a crucial marker for differentiating between euthyroidism and hyperthyroidism.

Table 2 and Figures 1 & 2 presents a comparison of Adipocytokines characteristics between the control and hyperthyroidism groups. Apelin levels were significantly higher in the hyperthyroidism group (284.4 ± 12.00 pg/mL) compared to the control group (229.3 ± 8.434 pg/mL) ($P = 0.0035$). Similarly, Lipocalin-2 levels were significantly elevated in the hyperthyroidism group (70.71 ± 5.772 pg/mL) compared to

Table 1. **Comparison of anthropometric and biochemical characteristics between the groups**

Parameters	Control ($n = 25$) Mean ± SED	Hyperthyroidism ($n = 35$) Mean ± SED	*P*-value (r^2)
Age (yr)	42.30 ± 2.857	40.86 ± 2.167	0.6893 (0.003)
TSH (IU/mL)	1.716 ± 0.1701	0.02020 ± 0.003928	<0.0001 (0.770)

Table 2. **Mean value of adipocytokines concentration in sera samples of control and patient groups**

Parameters	Control ($n = 25$) Mean ± SE	Hyperthyroidism ($n = 35$) Mean ± SE	*P*-value
Apelin (pg/mL)	229.3 ± 8.434	284.4 ± 12.00	0.0035
Lipocalin2 (pg/mL)	51.88 ± 1.504	70.71 ± 5.772	0.0279

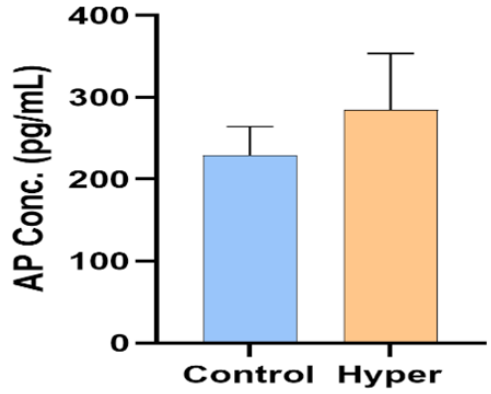

Fig. 1 **Mean value of Apelin concentration in sera samples of control and patient groups.**

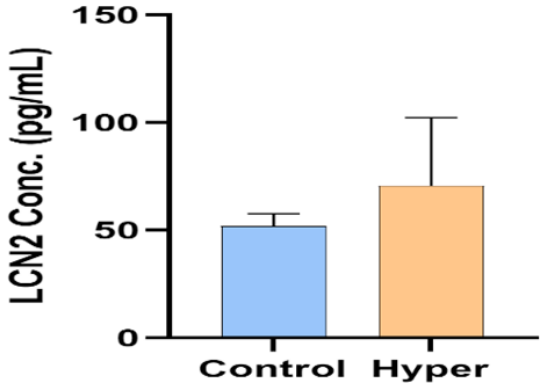

Fig. 2 **Mean value of Lipocalin2concentration in sera samples of control and patient groups.**

Table 3. **Mean value of growth factors concentration in sera samples of control and patient groups**

Parameters	Control ($n = 25$) Mean ± SE	Hyperthyroidism ($n = 35$) Mean ± SE	*P*-value
FGF-21 (pg/mL)	8.712 ± 0.206	15.76 ± 2.43	0.0339
VEGF (pg/mL)	26.21 ± 0.738	42.53 ± 5.34	0.0446

the control group (51.88 ± 1.504 pg/mL) ($P = 0.0279$). These findings suggest that both Apelin and Lipocalin-2 may be involved in the pathophysiology of hyperthyroidism.

Table 3 and Figures 3 & 4 presents a comparison of Growth factors characteristics between the control and hyperthyroidism groups. FGF-21 levels were significantly higher in the hyperthyroidism group (15.76 ± 2.43 pg/mL) compared to the control group (8.712 ± 0.206 pg/mL) ($P = 0.0339$). Similarly, VEGF levels were significantly elevated in the hyperthyroidism group (42.53 ± 5.34 pg/mL) compared to the control group (26.21 ± 0.738 pg/mL) ($P = 0.0446$). These findings suggest that both FGF-21 and VEGF may be involved in the pathophysiology of hyperthyroidism.

The Receiver Operating Characteristics Curve (ROC) Analysis

ROC analysis was conducted to evaluate the factors influencing the dependent variables for diagnosing hyperthyroid patients. The sensitivity of Apelin, Lipocalin-2, FGF-21, and

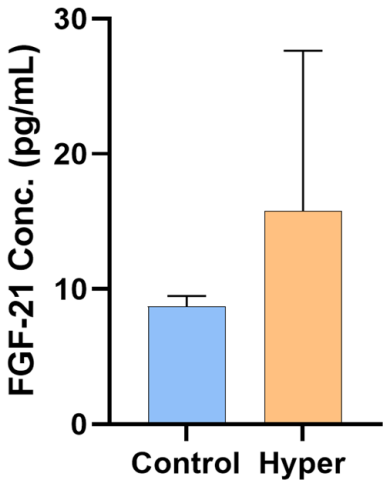

Fig. 3 **Mean value of FGF-21 concentration in sera samples of control and patient groups.**

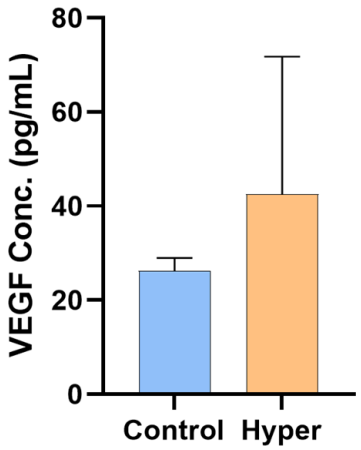

Fig. 4 **Mean value of VEGF concentration in sera samples of control and patient groups.**

VEGF as biomarkers for hyperthyroidism were 79%, 94%, 72%, and 81%, respectively, with specificities of 96%, 92%, 91%, and 84, respectively (Table 4, Figures 5–8).

Table 4 illustrates the AUCs, specificity, and sensitivity of all proinflammatory factors and adipokines in hyperthyroid patients relative to control subjects. An AUC of 0.9–1.0 indicates an excellent predictive value for a biomarker, 0.8–0.9 signifies a perfect marker, 0.6–0.7 denotes a good marker, and 0.6 reflects a negligible marker.

Figures 5–8 display the receiver operating characteristic curve (ROC) curve of AP, LCN2, FGF-21 performance as a potential diagnostic marker for Hyperthyroidism. A high area under the curve (AUC = 0.9033) for Lipocalin-2 suggests that it is an excellent biomarker for the diagnosis of hyperthyroidism. Similarly, the AUC for Apelin (AUC = 0.8125) and VEGF (AUC = 0.8095) indicates that these are very good biomarkers for detecting hyperthyroidism. Meanwhile, the AUC for FGF-21 (AUC = 0.7440) suggests that it is a good biomarker for the diagnosis of hyperthyroidism.

In hyperthyroid status, apelin has further significant statistical area under the ROC curve (AUC), (0.8125) as shown in Table 4 and Figure 5, the cut-off points and the corresponding validity tests values (sensitivity and specificity) for apelin in diagnosis of hyperthyroidism are showed a value of

Table 4. **The receiver operating characteristics curve (ROC) analysis**

Variables of ROC curve	Cut-off value	AUC	(95% CI)	SE	*P*-value	Sensitivity (%)	Specificity (%)
Apelin	260.24	0.8125	0.7148, 0.9616	0.03108	0.0004	84	96
LCN2	59.33	0.9033	0.8622, 0.9519	0.02081	<0.0001	94	92
FGF-21	10.12	0.7440	0.7013, 0.8697	0.04045	0.0131	79	91
VEGF	36.32	0.8095	0.7322, 0.9435	0.04203	0.0011	81	84

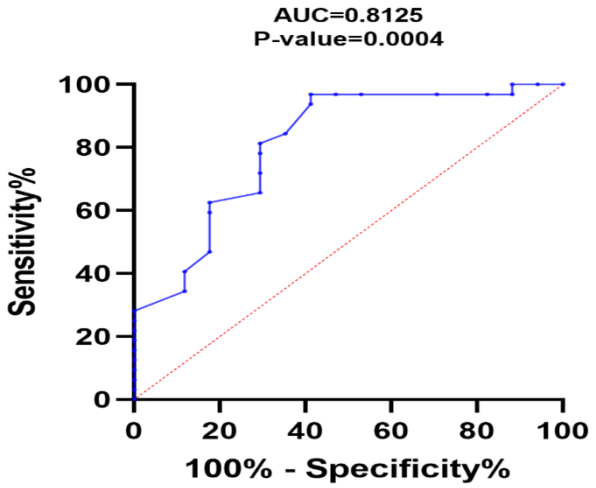

Fig. 5 **Receiver operating characteristic (ROC) curve results of serum Apelin.**

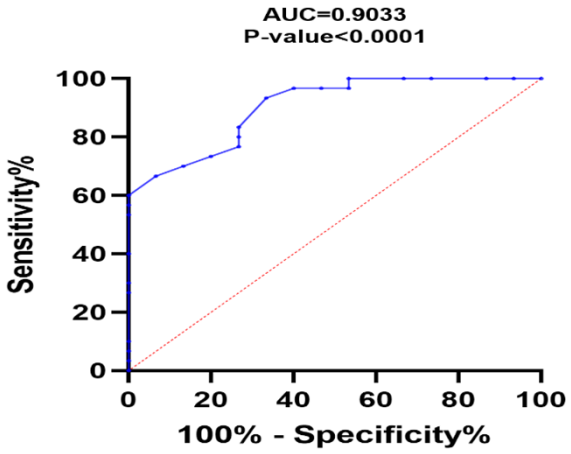

Fig. 6 **Receiver operating characteristic (ROC) curve results of serum LCN2.**

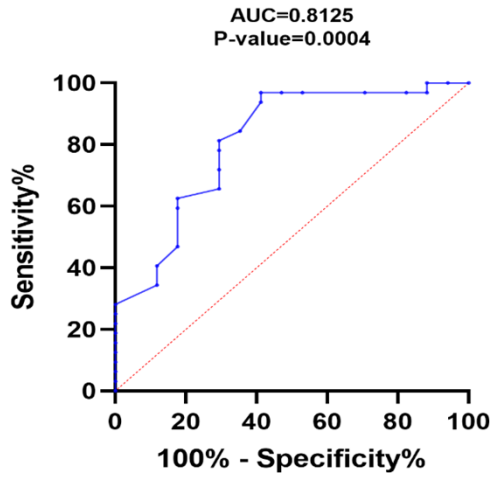

Fig. 7 **Receiver operating characteristic (ROC) curve results of serum FGF-21.**

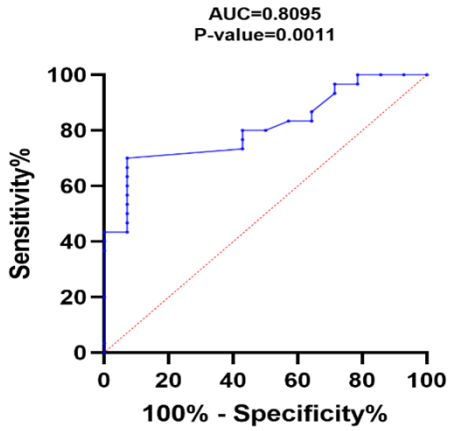

Fig. 8 **Receiver operating characteristic (ROC) curve results of serum VEGF.**

(260.24 pg/ml), with validity results: 84 percent sensitivity and 96 percent specificity in apelin levels]. There may thus be a connection between thyroid dysfunction and apelin since changes in thyroid hormones, and also TSH may impact the adipocytokines release.

In hyperthyroid status, area under the ROC curve (AUC) for (**LCN2**) and it was statistically significant for apelin ($P < 0.0001$), as provided in Table 4. The cut-off points and the corresponding validity tests values (sensitivity and specificity) for (LCN2) in diagnosis of hyperthyroidism was showed a value of 59.33 pg/mL), with validity results: 94 percent sensitivity and 92 percent specificity in apelin as shown in Table 4 and Figure 6.

In hyperthyroid status, **FGF-21** has further significant statistical area under the ROC curve (AUC), (0.7440) as shown in Table 4 and Figure 7, the cut-off points and the corresponding validity tests values (sensitivity and specificity) for **FGF-21** in diagnosis of hyperthyroidism are showed a value of (10.12/ml), with validity results: 79 percent sensitivity and 91 percent specificity in apelin levels]. There may thus be a connection between thyroid dysfunction and growth factor since changes in thyroid hormones, and also TSH may impact the growth factors release.

In hyperthyroid status, area under the ROC curve (AUC) for (**VEGF**) and it was statistically significant for apelin ($P < 0.0001$), as provided in Table 4. The cut-off

points and the corresponding validity tests values (sensitivity and specificity) for (**VEGF**) in diagnosis of hyperthyroidism was showed a value of 36.32 pg/mL), with validity results: 81 percent sensitivity and 84 percent specificity in apelin as shown in Table 4 and Figure 8.

Discussion

Serum Levels of Apelin

In this study there was significant increase in the level of apelin in hyperthyroidism patients, there may be a link between thyroid status, thyroid dysfunction, and adipocytokines. This is because variations in TSH and thyroid hormones may vary how adipocytokines are produced.[7]

While the significant role of the hypothalamus–pituitary-thyroid (HPT) axis in the regulation of thyroid hormones in the human body is well established,[17] the growing body of evidence points to the involvement of apelinergic system (apelin/APJ) in the HPT regulation.[17,18] Recent studies investigated the apelin levels in hypothyroidism patients. However, limited reports are available about its levels in hyperthyroidism patients. Adipose tissue, lungs, liver, heart, kidneys, the gastrointestinal system, brain, adrenal glands, the endothelium, and human plasma all express apelin.[19]

Two studies have evaluated apelin levels in patients with thyroid dysfunction. In both studies no significant difference was observed in serum apelin levels between patients with thyroid dysfunction and healthy control subjects.[7,20] The authors explained that these results were because, BMI was similar in both groups. In contrast to these findings, we observed significantly higher serum apelin levels in patients with hyperthyroidism.

In their study carried out in 2015, Gürel et al. (2015) examined the serum apelin levels in patients with thyroid dysfunction and found serum apelin levels higher than the control group.[7] Apelin receptors have been detected in the thyroid gland. Therefore, changes in the thyroid hormones and TSH may affect the release of adipocytokines, so there is a possible relationship between thyroid status, thyroid dysfunction and adipocytokines.[21]

It is known that there are TSH and thyroid hormone receptors in adipose tissue, and apelin receptors have been detected in the thyroid gland. Therefore, changes in the thyroid hormones and TSH may affect the release of adipocytokines, so there is a possible relationship between thyroid status, thyroid dysfunction and adipocytokines.[21]

Apelin is a hormone that plays an important role in many metabolic processes. Multiple factors can contribute to increased levels of apelin. Adipose tissue inflammation: Mild, persistent inflammation in adipose tissue is a hallmark of obesity. The inflammatory signal triggers an elevated release of various adipokines, such as apelin.[22]

Therefore, there is a clear association between adipocytokines, thyroid diseases, and thyroid function, as the release of adipocytokines can be affected by thyroid hormone and TSH levels.[21] Experiments investigating apelin-like bioactive peptides, including as leptin, adiponectin, resistin, and ghrelin, have varied results. Leptin (LEP) stimulates the thyroid gland via regulating specific receptors found in the paraventricular hypothalamus nucleus, this results in an increase in the release of thyrotropin-releasing hormone (TRH) in humans. Human leptin receptor mutations have been linked to central hypothyroidism.[23]

Serum Levels of Lipocalin-2 (LCN-2)

Levels of **Lipocalin-2** were significantly increased in patients compared to control. Our literature search did not identify any study which investigated lipocalin-2 levels among patients with hyperthyroidism; however, a limited number of studies exist which examined certain adipokines in patients with subclinical hypothyroidism and hypothyroidism. In our study, significant difference was observed between patients with hyperthyroidism and the control group in terms of serum lipocalin-2 levels. Aksoy et al. examined the levels of resistin (a member of adipokine family) among 36 female patients with subclinical hypothyroidism and 27 healthy female controls before and after 6 months of treatment with L-thyroxin. They found no difference before or after treatment.[24] Çinar et al. compared vaspin levels among 27 patients with overt hypothyroidism (33 patients with subclinical hypothyroidism and 41 healthy controls) and found no difference between them.[25] These results are consistent with ours. The aforementioned results might also suggest that there is no relationship between some of the members of adipokine family with the metabolic syndrome and/or with thyroid dysfunction.

On the other hand, some study results contradict ours. Jing et al., comparing levels of visfatin (an adipokine) among hypothyroid and hyperthyroid patients and euthyroid subjects, found significantly higher plasma visfatin levels in their hypothyroidic and hyperthyroidic patients.[26] They repeated the same study using an animal model of Wistar rats and showed that serum visfatin levels were significantly higher in hypothyroid animals compared to euthyroidic animals.[26] The significant difference might have resulted from the absence of subjects with subclinical hypothyroidism and inclusion of patients with overt hypothyroidism. Conversely, a similar relationship with subclinical hypothyroidism may be present due to the fact that subclinical hypothyroidism is a predisposing condition and a milder form of hypothyroidism.

Serum Levels of Fibroblast Growth Factor 21 Levels

In the current study, we demonstrated that hyperthyroid patients had significantly higher serum FGF21 levels as compared with normal controls. These findings provide an insight into clinical implication of FGF21 in hyperthyroid patients. This result was in line with[27] who documented that higher levels of serum FGF21is seen in patients with hyperthyroidism healthy control. These findings provide an insight into clinical implication of FGF21 in hyperthyroid patients.

Numerous studies on serum FGF21 levels in patients with thyroid dysfunction have shown variable results. A study conducted by Fangsen Xiao *et al*. showed that serum FGF21 levels were elevated in patients with hyperthyroidism and declined after thionamide treatment, and serum FGF21 level was independently associated with hyperthyroidism.[27]

We found that serum FGF21 levels were markedly elevated in patients with hyperthyroidism compared to healthy age and sex-matched healthy controls which is in concordance with study done by Fangsen Xiao *et al*., but the serum FGF21 levels in patients with hyperthyroidism were relatively higher in our study than their study.[27] In contrast, a study done by Bonde *et al*. showed that in humans, FGF21 serum levels were

unaltered in hyperthyroidism, but that study was limited by small sample size and lack of normal controls.[28] A study conducted by Guang Wang *et al*. showed that the patients with overt hypothyroidism had significantly lower FGF21 levels.

FGF21, a member of endocrine FGF family, emerged as a hormone involved in the regulation of glucose, lipid, and energy metabolism which share great similarities with the metabolic actions of thyroid hormones. In the current study, we demonstrated that hyperthyroid participants had higher serum FGF21 levels than the controls. The mechanisms by which serum FGF21 levels are increased in hyperthyroid individuals are unclear. One possible explanation is that the increase in serum FGF21 levels might be a compensatory mechanism in response to altered metabolism by thyroid hormones such as changed basal metabolic rate or body fat accumulation. Alternatively, the increase in serum FGF21 levels might be a response to local regulation by thyroid hormones.[29] Thyroid hormones synthesis is under the influence of many systemic factors and local factors, which include the actions of deiodinases that convert T4 to T3. Therefore, an increase in hepatic deiodinase activity, promoting a local increase in T3, might account for increased FGF21 synthesis in the liver. Lastly, although the mechanism of FGF synthesis and clearance is unclear, the elevation of serum FGF21 in hyperthyroid individuals might arise from an altered balance between synthesis and clearance of FGF21.[29]

Circulating Vascular Endothelial Growth Factors Concentration

Vascular Endothelial Growth Factors levels were significantly elevated in patients than in control. Several studies on VEGF expression in thyroid glands with thyroid dysfunction have been reported.[30,31] However, in vivo expression and localization of VEGF in thyroid dysfunction have not been studied extensively.

Expression of VEGF is regulated by many factors.[32,33] In thyroid glands, it has been reported that TSH and Graves IgG upregulate VEGF-mRNA expression.[34] Suzuki et al.[35] Reported that follicular thyroglobulin suppressed VEGF-mRNA expression in rat normal thyroid cell line (FRTL-5). From this finding, it is conceivable that follicular thyroglobulin (colloid) depletion in thyroid dysfunction tissues may enhance VEGF-mRNA expression.

It is well known that there is marked enlargement of the blood capillaries and an increase in blood flow in the thyroids of hypothyroid animals[36] and thyroid dysfunction.[37] It has been demonstrated in vitro that vascular endothelial growth factor (VEGF), an endothelial cell-specific angiogenic factor, is produced by thyroid follicular epithelial cells in response to stimulation of the TSH receptor.[38,39] Secreted VEGF then stimulates Flt receptors (receptors for VEGF) on endothelial cells in a paracrine manner, leading to proliferation of the endothelial cells and hypervascularity of the thyroid gland. VEGF, therefore, may be one of the important thyroids angiogenic factors. In this study we have evaluated serum VEGF levels in patients with hyperthyroidism. We found a significant increase in serum VEGF levels in patients with hyperthyroidism. There was a significant increase in intrathyroidal vascular area in patients with thyroid dysfunction. This suggests that the mechanism of the increase in serum VEGF in these patients may be different. Sato et al. reported that TSH and thyroid-stimulating antibodies stimulated the expression of VEGF messenger ribonucleic acid in vitro in thyroid epithelial cells.[40] The VEGF then stimulated vascular endothelial cells in the thyroid, resulting in increases in blood vessels and thyroid volume.[40]

Receiver Operating Curve (ROC) of Serum Adipocytokines and Growth Factors Levels to Diagnosis of Hyperthyroidism Cases

The diagnostic effectiveness of adipocytokines and growth factor levels in differentiating individuals with hyperthyroidism from healthy individuals was evaluated through analyzing the receiver operating characteristic (ROC) curve. Figures 5–8 indicate that the area under the curve (AUC) for all four parameters was significantly below 0.05.

In the results of the (ROC) curve and the (AUC) study for Lipocalin-2 besides their ratio as possible diagnostic parameters. Lipocalin-2 was shown an excellent diagnostic performance for prediction hyperthyroid Patients compared to control group; data is presented in Figure 6. The ROC curves analysis for serum Lipocalin-2 level, when used as test for diagnosis individuals into hyperthyroidism and control groups revealed the (AUC = 0.9033; $P < 0.0001$)

To assess the predictive values of other studied biomarkers FGF-21, VEGF and Apelin, ROC curve analyses were performed in patients with hyperthyroidism. Figures (5, 7 and 8) demonstrates the scatter dot graphs of serum FGF-21 (AUC = 0.7440; *P*-value = 0.0004), VEGF (AUC = 0.8095; *P*-value = 0.0011), apelin (AUC = 0.8125; *P*-value = 0.0004). The scatter graphs highlight the very good diagnostic performance for both apelin and VEGF with good diagnostic performance for FGF-21.

Limitations of the Study

The main limitation of the current study is the relatively limited number of participants (the sample size). Another limitation of our study is that we did not calculate the correlation of T_3&T_4 with main studied parameters. Altered levels of Adipocytokines and Growth factors in hyperthyroid patients may suggest Adipocytokines and Growth factors are two of the many key molecules that are regulating thyroid function. Nonetheless, further analysis and larger studies are needed to clarify the role of Adipocytokines and Growth factors in the pathogenesis of hyperthyroidism.

Conclusion

Based on the results obtained from this study and ROC curve analysis, it is concluded that alterations in levels of Adipocytokines and Growth factors may contribute to the early diagnosis of hyperthyroidism. More clinical and experimental scientific studies should be conducted on this subject. Whether the impact of thyroid dysfunction on the levels of Adipocytokines and Growth factors persist in the whole thyroid function spectrum deserves further investigation.

Availability of Data and Materials

The data used to support the findings of this study are available from the corresponding author upon request.

Author Contributions

The study was designed by Hardam Mohammed and Parween Abdulsamad. Data acquisition and collection was by Hardam Mohammed. Data analysis was by Hardam Mohammed and Parween Abdulsamad, and literature search and manuscript preparation was by Parween Abdulsamad. The manuscript was edited by Hardam Mohammed and Parween Abdulsamad, and reviewed by Parween Abdulsamad take responsibility for the integrity of the work.

Ethics Approval and Consent to Participate

The Ethics Committee of Salahaddin University accepted this study (13795). Ethical consent statements were obtained for all participating persons, in alignment with the Helsinki Declaration established by the World Medical Association, most recently updated in Edinburgh in 2008.

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Disclosure of Conflict of Interest

The authors declare no conflict of interest.

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