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FULL PAPER

Association of serum apelin and atherogenic indices in patients with primary thyroid diseases

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Apelin is an adipocytokine secreted from adipocytes. Although much research has been conducted on apelin, no or few reports are there about its association with atherogenic indices in patients with thyroid dysfunctions. The aim of this study is to investigate the association between serum apelin and atherogenic indices. A total of 177 participants were included in the current study (43 controls and 124 patients with thyroid dysfunction). Serum apelin and lipid profile tests were determined and atherogenic indices were calculated for each participant. Higher concentrations of Apelin level in hyperthyroidism were compared with control groups and hypothyroidism. All types of an atherogenic indices indicated a significant increase in hypothyroidism more than hyperthyroidism and control groups, the atherogenic indices (AIP, CRI-I, CRI-II, AC, and Chol indices) had more diagnosis accuracy than apelin in a diagnosis of hypothyroidism group, despite of that apelin had more diagnosis accuracy than atherogenic indices (AIP, CRI-I, CRI-II, AC, and Chol indices) in a diagnosis of hyperthyroidism group. The apelin was significantly increased in hyperthyroidism compared with hypothyroidism.

KEYWORDS

Apelin; atherogenic; hyperthyroidism; hypothyroidism diagnostic accuracy; dyslipidemia.

Introduction

Thyroid hormones exert their physiological action on nearly all nucleated cells and they are essential for lipid metabolism and growth [1]. Hyperthyroidism occurs when the thyroid gland produces and secrets excessive amounts of thyroid hormones [2]. Epidemiologically, the overall hyperthyroidism prevalence among Europeans is 0.8% and overt hyperthyroidism ranges between 0.5-0.8% [3,4]. Besides, it affects 1.3% of the US population with only 0.5% of cases as overt hyperthyroidism [5]. However, hyperthyroidism is five times more common in females than in males, and its prevalence increases to 4-5% in elderly women [5]. The hyperdynamic cardiovascular state can be induced by hyperthyroidism and associated with systolic hypertension, tachycardia, atrial fibrillation, and increased CVD mortality [6].

In addition, a recent study by Shafeeq (2019) found that dyslipidemia can be associated with hyperthyroidism [7]. The APJ, a novel G protein-coupled receptor, which is identified in 1993 by O'Dowd *et al.* [8] and its legend "apelin" which is isolated and characterized by are both found to participate in the regulation of endocrine signals that affect the biological functions such as metabolism and stress [9,10]. While the significant role of the hypothalamus–pituitary-thyroid (HPT) axis in the regulation of thyroid hormones in the human body is well established [11], the growing body of evidence points to the involvement of apelinergic system (apelin/APJ) in the HPT regulation. 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. Apelin-36 predominates in the lung, testis, and uterus, whereas apelin-13 and apelin-36, to a lesser extent, have been regarded as the most active isoforms having the most action on the cardiovascular system [12]. Apelin has a wide range of biological effects, including nitric oxide (NO)-induced hypotension, angiogenesis, cardiac contractility stimulation, water intake, diuretic action [13], angiotensin II antagonistic effects, endothelium-dependent vasodilatation, direct vasoconstriction on smooth muscle, positive inotropes, nitric oxide-dependent diuretic impact, and other cardiovascular activities of the apelin-receptor system have all been documented. These results have sparked research into the role of apelin as an endogenous mediator, which is important for cardiovascular disorders [13]. In addition to act as energy storage cells, adipocytes are biologically active cells that make peptides called adipocytokines, which have physiological effects. Adipocytokines control several physiological processes including nutrition, thermogenesis, immunity, thyroid and reproductive hormones, and neuroendocrine activity. One of the most important new family members is Apelin [14].

Separately, many reports have recently shown that the traditional lipid tests (e.g., total cholesterol (TC), triglycerides (TGs), high-density lipoprotein (HDL)-cholesterol, and low-density lipoprotein (LDL)-cholesterol) may remain unchanged even in confirmed cases with CVD [15-17]. On the other hand, atherogenic indices and lipid ratios [atherogenic index of plasma (AIP), Castelli's Risk Indexes (CRI-I and CRI-ii), atherogenic coefficient (AC), and cholesterol index (Cholindex)] have shown a significant efficiency in recognizing certain diseases related to cardiovascular dysfunctions [18]. In this context, several reports have also revealed that atherogenic indices are better predictors of CVD risk than traditional lipid tests [18,19]. However, atherogenic indices in hyperthyroidism patients were yet to be fully elucidated. This study is sought to explore plasma apelin levels, atherogenic indices and their association to each other as well as the diagnostic accuracy of apelin as a predictor of thyroid dysfunction in Iraqi population.

Materials and methods

A case-control study of (177) participants were included, 71 patients with hyperthyroidism (19 males and 52 females) and 53 with hypothyroidism (40 females and 13 males), who diagnosed at Al-Faiha'a specialized Diabetes Endocrine and Metabolism Center, Basra Health Directorate, Iraq; during the period between (15 September 2019 to March 2020). The endocrinologist at the center examined and confirmed all the participants' cases as well as apparently healthy age-matched participants as controls. Other acute and chronic renal diseases such as diabetes

mellitus, cardiovascular, hepatic, and renal diseases were excluded.

The College of Health and Medical Technology (Basrah, Iraq) approved the current study and its protocols as well as the Al-Faiha Specialized Diabetes, Endocrine, and Metabolism Center and Basrah Health Directorate Ethics Committee. In addition, written informed consent was obtained from each participant before the enrollment in the study.

A blood sample was collected from each participant. To determine the serum apelin concentration, the commercial ELISA kit from Elabscience (E-EL-H0458, Texas, the USA) was used. Serum lipids profile (total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, very low-density lipoprotein cholesterol, and triglycerides) levels were measured spectrophotometrically in all samples using Spinreact commercial kits, Spain.

Atherogenic indices were calculated mathematically using formulas reviewed by Adedokun *et al.* [17], as follows:

1- $AIP = \log\left(\frac{\text{HDL-c}}{\text{LDL-c}}\right)$

2- $\text{CRI-I} = \frac{\text{TC}}{\text{HDL-c}}$

3- $\text{CRI-II} = \frac{\text{LDL-c}}{\text{HDL-c}}$

4- $AC = \frac{\text{TC - HDL-c}}{\text{HDL-c}}$

5- $\text{Chol-index}_{(mg/dL)}$ = LDL-c – HDL-c (or = LDL-c – HDL-c – VLDL-c for those with TGs ≥400 mg/dL).

GraphPad Prism 8 software, the USA, was used to conduct the comparisons between the means of two groups (using Mann-Whitney's U test) and correlation analysis (using Spearman's correlation), while receiver operating characteristic (ROC) curve analysis was performed using MedCalc software (MedCalc Software, Belgium) to assess the diagnostic accuracy of apelin in thyroid diseases, statistically significant *p-value* < 0.05.

Results and discussion

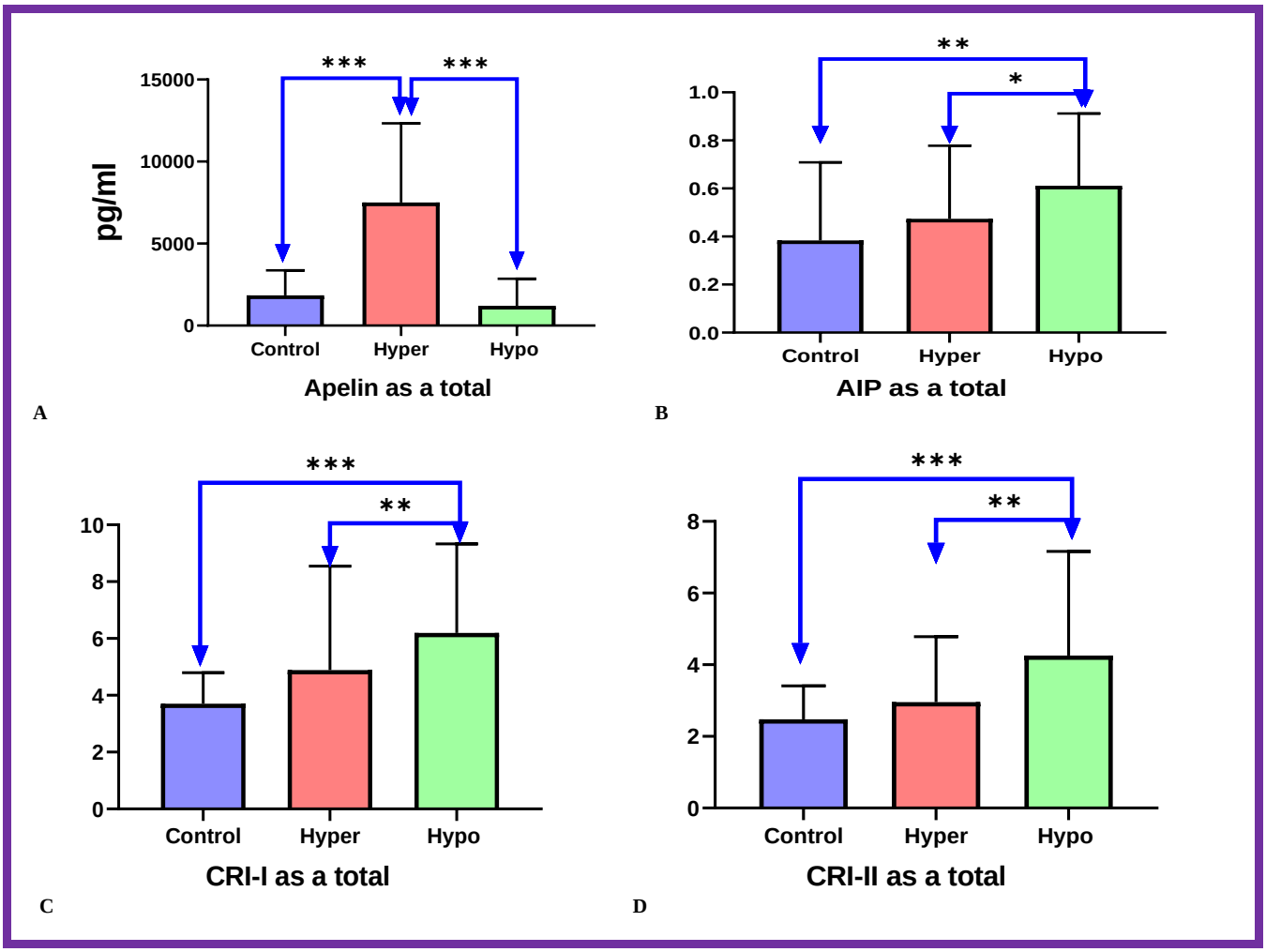
In this study as shown in Table 1 there was no significant difference in age as total, male and female P-value> 0.05,also in table 2 shown that all Atherogenic indices and apelin shown significant difference P – value < 0.05 expect AIP as a male P-value 0.356, as compared between study groups.

TABLE 1 Anthropometric data

		Control (n=43)	Hyperthyroidism (n=71)	Hypothyroidism (n=53)	P-value
Age (years old)	**Males**	37.96±9.653	38.37±9.136	37.54±8.589	0.969
	Females	36.26±8.806	35.73±10.75	38.08±10.29	0.548
	Total	37.21±9.218	36.44±10.35	37.94±9.822	0.702
Males		**24**	**19**	**13**	
Females		**19**	**52**	**40**	0.002
Total		**43**	**71**	**53**	

TABLE 2 Biomarkers

		Control (n=43)	Hyperthyroidism (n=71)	Hypothyroidism (n=53)	*P-value*
Apelin	**Male**	1318(2514-486.8)	8627(10248-1612)	631.0(1355-499.2)	<0.001
	Female	933.0(3066 - 802.0)	5997(12299 - 3499)	643.1(1123 -563.5)	<0.001
	Total	1795±1564	7402±5029	1412±2132	<0.001
AIP	**Males**	0.4394±0.3354	0.5526±0.2977	0.5856±0.3609	0.356
	Females	0.3142±0.3047	0.4455±0.3037	0.6196±0.2829	<0.001
	Total	0.3841±0.3246	0.4741±0.3038	0.6113±0.3005	0.002
CRI-I	**Males**	4.143±1.187	5.064±2.443	6.258±2.668	0.016
	Females	3.151±0.6188	4.823±4.027	6.175±3.300	<0.001
	Total	3.705±1.088	4.888±3.655	6.195±3.132	<0.001
CRI-II	**Males**	2.817±0.9545	3.145±1.534	4.401±2.219	0.013
	Females	2.042±0.7155	2.890±1.932	4.213±3.120	<0.001
	Total	2.475±0.9326	2.958±1.827	4.259±2.906	<0.001
CHOL-index	**Males**	68.26±34.38	56.49±30.15	121.1±93.18	0.004
	Females	50.98±34.83	51.87±82.16	112.9±78.92	<0.001
	Total	60.63±35.25	53.11±71.80	114.9±81.77	<0.001
AC	**Males**	3.143±1.187	4.064±2.443	5.258±2.668	0.016
	Females	2.151±0.6188	3.823±4.027	5.175±3.300	<0.001
	Total	2.705±1.088	3.888±3.655	5.195±3.132	<0.001



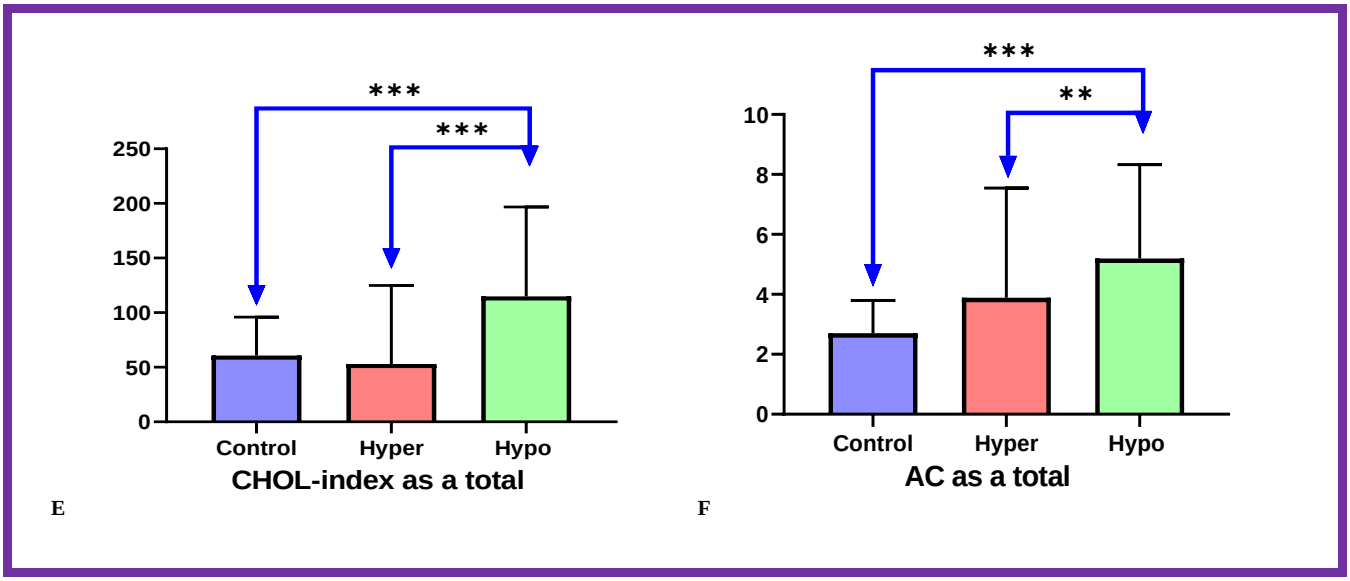


FIGURE 1 Explanation of the significant behavior between the patient groups and the control group and between groups with each other, using post hoc-test. The bars indicate: mean ± standard deviation.

*: *P-value* = 0.033 **: *p-value* = 0.002 ***: *p-value* < 0.001.

The most prevalent endocrine condition in the world after diabetes is hypothyroidism, which is among thyroid diseases that are quite widespread worldwide. Compared with hypothyroidism, thyrotoxicosis is less common. Weight fluctuations, thermogenesis, and adipose tissue lipolysis are all seen in people with thyroid dysfunction. Hypothyroidism patients often gain weight, experience a drop in body temperature, and have a slower metabolic rate. In contrast, weight loss occurs in hyperthyroidism patients despite having a faster metabolic rate and increased hunger. The alterations in adipose tissue are mostly to blame for these metabolic disparities [14]. Therefore, the apelin level in hyperthyroidism group reported significantly increased p-value < 0.05 compared with the control as displayed in (Figure 1 A) (7402±5029 vs. 1795±1564 pg/ml, in hyperthyroidism and control, respectively). This result of the study was agreed with [14], while in the hypothyroidism group, it was not significant, *p-value* > 0.05 (1412±2132 vs. 1795±1564 pg/ml, respectively); as listed in (Table 2). Reduced resting heart rate, cardiac output, cardiac contractility, stroke volume, systemic resistance, and diastolic pressure were all reported in hypothyroidism, in addition to the narrow pulse of bradycardia. Hypothyroidism contributes to certain structural and morphological changes in cardiac cells that result in changes in heart hemodynamic properties [20]. In hypothyroid patients, prolonged PR and QT intervals and flattening or reversing waves were noted. Electrocardiogram manifestations such as sinus bradycardia complexes were in low voltage. Pericardial effusion in up to 30 percent of hypothyroid patients, which may affect ECG, has also been documented [21]. Among the most effective endogenous inotropic positive agents are apelin peptides. The apelin-mediated inotropic activity by combination with a APJ receptor stimulates protein kinase C, affecting Na^{+}/H^{+} exchanger, and thus this promotes inner cell alkalinisation and myofilament sensitization to Ca^{++} [22]. This study disagreed with [14], who found that the hypothyroid group had the highest and the

control group had the lowest mean apelin levels, while some studies such as [23], since apelin levels were shown to be low in the subclinical hypothyroidism group, 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 [14].

In this study, AIP was significantly different, *p-value* <0.05 in total patients and in females when compared hypothyroidism and control groups, as indicated in Figure 1 B. Previous studies such as [24],[25] found that AIP was significantly increase, *p-value* <0.05, when compared subclinical hypothyroidism and euthyroid groups. This study agreed with study [26]. Duo to thyroid hormone regulates the synthesis and metabolism of lipids by decreasing intestinal cholesterol absorption and increasing hepatic cholesterol synthesis. The increased AIP indicating an atherogenic risk profile, as these were considered as useful indices to identify subjects carrying cardiovascular disease risk [25].

The current study revealed that CRI-I and CRI-II were significantly increased, *p-value* <0.05 as total, males and as females when compared hypothyroidism with control groups as displayed in Figure 1 C&D; this study agreed with [27] and disagreed with [26], also CRI-I was significantly increased, *p-value* <0.05 as female only when compared hyperthyroidism with control groups as presented in Table 2. AC was significantly increased, *p-value* <0.05 as total, males and females when compared hypothyroidism and hyperthyroidism with control groups as depicted in Figure 1 f, this study was agreed with [26]. Likewise, AC was significantly increased, *p-value* <0.05 as female only when compared hyperthyroidism with control groups as showed in Figure 1 F.

TABLE 3 Analysis of the Receiver-operating Characteristic (ROC) curve for the value of apelin levels and atherogenic index for the hyperthyroidism group diagnosis

Index	Cut-off value	Sensitivity % (95% CI)	Specificity % (95% CI)	+PV	-PV	Accuracy	AUC
AIP	>0.363	70.42 (58.4 - 80.7)	48.84 (33.3 - 64.5)	66.3	69.2	0.1926	0.556
CRI-I	>4.212	53.52 (41.3 - 65.5)	76.74 (61.4 - 88.2)	79.2	50.0	0.3027	0.634
CRI-II	≥0.0439	100 (94.9 - 100.0)	0 (0.0 - 8.2)	62.3	0	0.2548	0.557
AC	>3	59.15 (46.8 - 70.7)	69.77 (53.9 - 82.8)	76.4	50.8	0.3027	0.634
Chol-index	>190	100.00 (94.9 - 100.0)	0 (0.0 - 8.2)	62.3	0	0.1562	0.532
Apelin	>2867	80.28 (69.1 - 88.8)	81.40 (66.6 - 91.6)	87.7	71.4	0.6443	0.870

TABLE 4 Analysis of the Receiver-operating Characteristic (ROC) curve using the atherogenic index and apelin values to diagnose hypothyroidism in a group

Index	Cut-off value	Sensitivity % (95% CI)	Specificity % (95% CI)	+PV	-PV	Accuracy	AUC
AIP	>0.308	88.68 (77.0 - 95.7)	42.86 (27.7 - 59.0)	66.2	75.0	0.3239	0.689
CRI-I	>4.459	73.58% (59.7 - 84.7)	83.72 (69.3 - 93.2)	84.8	72.0	0.5774	0.796
CRI-II	>3.260	62.26 (47.9 - 75.2)	88.37 (74.9 - 96.1)	86.8	65.5	0.5064	0.739
AC	>3.459	73.58 (59.7 - 84.7)	83.72 (69.3 - 93.2)	84.8	72.0	0.5774	0.796
Chol-index	>117	49.06 (35.1 - 63.2)	100 (91.8 - 100.0)	100	61.6	0.4906	0.73
Apelin	≤1607	86.79 (74.7 - 94.5)	46.51 (31.2 - 62.3)	66.7	74.1	0.3330	0.659

In hyperthyroid status, apelin has further significant statistical area under the ROC curve (AUC), (0.870) as shown in (Table 3 and Figure 2), The cut-off points and the corresponding validity tests values (sensitivity and specificity) for apelin in diagnosis of hyperthyroidism are showed a value of (>2867 pg/ml), with validity results: 80.28 percent sensitivity and 81.40 percent specificity in apelin levels that were greater than those in the control group [14,28]. 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 hypothyroid status, area under the ROC curve (AUC) for apelin (0.659) and it was statistically significant for apelin (p-value <0.05), as provided in (Table 4). The cut-off points and the corresponding validity tests values (sensitivity and specificity) for apelin in diagnosis of hypothyroidism was showed a value of (≤1607 pg/ml), with validity results: 86.79 percent sensitivity and 46.51 percent specificity in apelin as shown in (Table 4).

The atherogenic indices (AIP, CRI-I, CRI-II, AC, and Chol indices) had more diagnosis accuracy than apelin in a diagnosis of hypothyroidism group, despite of that apelin had more diagnosis accuracy than atherogenic indices (AIP, CRI-I, CRI-II, AC, and Chol indices) in a diagnosis of hyperthyroidism group, as demonstrated in Figure 2, illustrated that apelin had more diagnosis accuracy in hyperthyroidism more than hypothyroidism groups. When compared with other lipid markers, the AUC for CRI-I and AC in the hypothyroidism group were the greatest and statistically significant (0.796 and 0.796, respectively). This research supports [26].

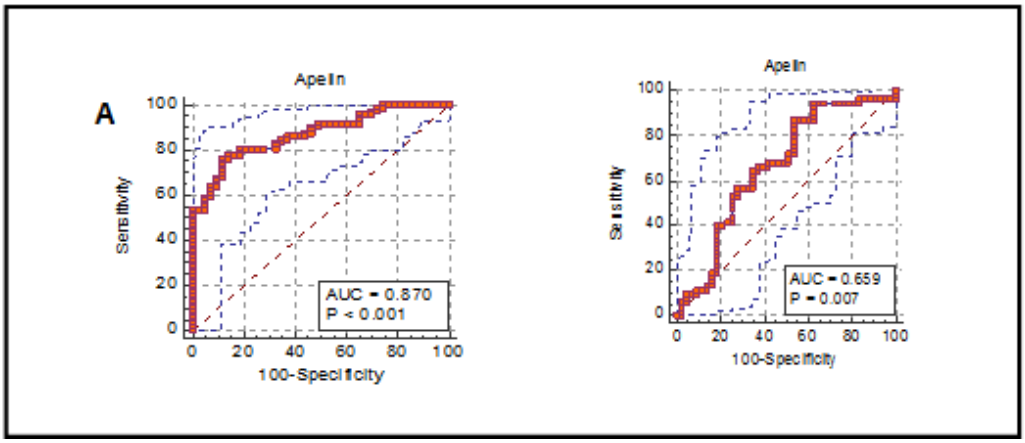


FIGURE 2 Area under the ROC curve for apelin levels as A-hyperthyroidism group B- hypothyroidism group

Conclusion

The study concluded that apelin level was significantly increased in hyperthyroidism compared with hypothyroidism and control groups. In addition, apelin is considered as a good indicator (AUC= 0.87) for diagnosis accuracy of hyperthyroidism patients, all types of an atherogenic indices demonstrated the significant increase in hypothyroidism more than hyperthyroidism and control groups, the atherogenic indices (AIP, CRI-I, CRI-II, AC, and Chol indices) had more diagnosis accuracy than apelin in a diagnosis of hypothyroidism group, despite of that apelin had more diagnosis accuracy than atherogenic indices (AIP, CRI-I, CRI-II, AC, and Chol indices) in a diagnosis of hyperthyroidism group.

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Conflict of Interest

The authors have no conflict of interest.

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