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Serum Lipocalin-2 Levels in Obese Iraqi Women with Hypothyroidism: Associations with Thyroid Function, Lipid Profile, and Diagnostic Implications

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Abstract

Lipocalin-2 (LCN-2) is a glycoprotein that mediates inflammation and innate immunity, among other biological functions. The study aimed to evaluate LCN-2 levels in obese women, with and without hypothyroidism, to investigate the relationship between LCN-2 levels and BMI and thyroid hormones. Also, to explore the relevance of its level as a diagnostic parameter in these patients. The cross-sectional study involved 140 women aged 18-45 years, divided into four groups of 35: a healthy control (C) group, an obese (H1) group, a newly diagnosed hypothyroid (H2) group, and an obese hypothyroid (H3) group. The BMI, fasting blood glucose (FBG), HbA1c, thyroid hormones, lipid profiles, and LCN-2 levels were assessed for all participants. Results indicated a significant increase in BMI (Kg/m^2) among H1 and H3 compared to the C and H2 groups. The levels of FBG, HbA1c, TSH, total cholesterol (TC), triglycerides (TG), LDL, VLDL, AIP and Non-HDL were significantly higher ($p < 0.05$) in the H3 group compared to the H1 and C groups, while T3, T4, and HDL levels were significantly lower. The H3 group showed ($p < 0.05$) a higher LCN-2 level ($7.38 \pm 1.80 \text{ ng/ml}$) compared to other groups C, H1 and H2 (3.51 ± 0.99 , 6.03 ± 1.17 and 4.20 ± 0.82 , respectively). A significant positive correlation was found between LCN-2 and BMI in all patient groups. Also, a positive correlation between LCN-2 and TSH was noted in H3 and H2 groups, while a negative correlation with T3 and T4 was noted in the H3 group. For diagnostic discrimination, LCN-2 achieved AUC values of 0.943, 0.883, and 0.976 in comparisons of C versus H1, H2, and H3, respectively. Elevated serum LCN-2 levels are associated with BMI in obese Iraqi women with and without hypothyroidism. LCN-2 may represent a potential biomarker for female obesity, particularly in cases of hypothyroidism. However, further validation in larger, longitudinal studies is needed to confirm these results. This study has some limitations because of its cross-sectional design, small sample size, and lack of free T3/T4, which may limit the interpretation of thyroid function dynamics.

Keywords: Lipocalin-2, Hypothyroidism, Obesity, Lipid profile, Body mass index.

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مستويات ليبوكالين-2 في مصل الدم لدى النساء العراقيات البدينات المصابات بقصور الغدة الدرقية: الارتباطات مع وظيفة الغدة الدرقية، وملف الدهون، والآثار التشخيصية

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الخلاصة

ليبوكالين-2 (LCN-2) هو بروتين سكري له دور في العمليات البايولوجية المختلفة، وخاصة الالتهابات والمناعة الفطرية. هدفت الدراسة إلى تقييم مستويات LCN-2 لدى النساء البدينات، المصابات وغير المصابات بقصور الغدة الدرقية، وذلك لدراسة علاقة مستواه بمؤشر كتلة الجسم وهرمونات الغدة الدرقية. كذلك، استكشف أهمية مستواه كميّار تشخيصي لدى هؤلاء المرضى. شملت الدراسة المقطعية 140 امرأة تتراوح أعمارهن بين 18 و45 عامًا، مقسمات إلى أربع مجموعات، كل مجموعة تضم 35 امرأة: مجموعة ضابطة سليمة (C)، ومجموعة مصابة بالسمنة (H1)، ومجموعة مصابة حديثاً بقصور الغدة الدرقية (H2)، ومجموعة مصابة بقصور الغدة الدرقية والسمنة (H3). تم تقييم مؤشر كتلة الجسم، وسكر الدم الصائم (FBG)، وHbA1c، وهرمونات الغدة الدرقية، ومستويات الدهون، ومستويات LCN-2 لجميع المشاركات. أشارت النتائج إلى زيادة كبيرة في مؤشر كتلة الجسم (Kg/m^2) لدى مرضى السمنة وقصور الغدة الدرقية مع السمنة مقارنةً بمجموعتي الضابطة وقصور الغدة الدرقية. كانت مستويات FBG وHbA1c وTSH والكوليسترول الكلي (TC) والدهون الثلاثية (TG) وLDL وVLDL وAIP وnon-HDL أعلى بكثير ($p < 0.05$) في مجموعة قصور الغدة الدرقية مع السمنة مقارنةً بمجموعتي السمنة والتحكم، بينما كانت مستويات T3 وT4 وHDL أقل بكثير. أظهرت مجموعة قصور الغدة الدرقية مع السمنة مستوى LCN-2 (ng/ml) أعلى بكثير (7.38 ± 1.80) مقارنةً بالمجموعات الأخرى، التحكم (3.51 ± 0.99) و السمنة (6.03 ± 1.17) وقصور الغدة الدرقية (4.20 ± 0.82). هناك ارتباط إيجابي كبير بين LCN-2 ومؤشر كتلة الجسم في جميع مجموعات المرضى. أيضًا، لوحظ وجود ارتباط إيجابي بين LCN-2 وTSH في مجموعات قصور الغدة الدرقية مع السمنة ومجموعة قصور الغدة الدرقية بينما كان هناك ارتباط سلبي مع T3 وT4 في مجموعة قصور الغدة الدرقية المصابة بالسمنة. لأغراض التشخيص، أظهر LCN-2 قيم المساحة تحت المنحنى (AUC) 0.943 و0.883 و0.976 عند مقارنة مجموعة التحكم بمجموعات السمنة وقصور الغدة الدرقية وقصور الغدة الدرقية المصابة بالسمنة على التوالي. وبالتالي، ترتبط مستويات LCN-2 المرتفعة في المصل بمؤشر كتلة الجسم لدى النساء العراقيات البدينات، سواء كن مصابات بقصور الغدة الدرقية أم لا. قد يُمثل LCN-2 مؤشرًا حيويًا محتملاً للسمنة لدى النساء، وخاصة في حالات قصور الغدة الدرقية. ومع ذلك، هناك حاجة إلى مزيد من التحقق في دراسات طولية أوسع نطاقاً لتأكيد هذه النتائج. تحتوي هذه الدراسة لبعض من القيود نظرًا للتصميم المقطعي، وصغر حجم العينة، ونقص بيانات هرمونات الغدة الدرقية الحرة T3/T4، مما قد يحد من تفسير ديناميكية وظيفة الغدة الدرقية.

1. Introduction

Hypothyroidism is an endocrine condition caused by inadequate production and release of glandular thyroid hormones and their corresponding metabolic disturbances. Patients generally complain of fatigue and lethargy and often show intolerance to cold; they also tend to gain weight. These symptoms are due to a decline in the basal metabolic rate and thermogenesis [1]. The condition is more prevalent in women than men, with the estimated incidence being 5 to 20 times higher in women than in men [2]. The condition is diagnosed after assessing the hormones released by the thyroid gland and measuring their levels in the

blood [3]. Obesity is classified as a chronic inflammatory state which can be chronic and can be assessed by determining the body mass index (BMI) and measuring the waist circumference (WC) to assess and manage it. The association between obesity and hypothyroidism is becoming increasingly studied [4]. It is already established that hypothyroidism is associated with a higher BMI and increased obesity [5].

Hypothyroidism is a prominent contributor to hypercholesterolemia, which is characterized by elevated levels of low-density lipoprotein cholesterol (LDL-C). This condition arises from a diminished catabolism of LDL, attributable to a reduction in the number of LDL receptors on the surfaces of liver cells, a process mediated by triiodothyronine (T3). Furthermore, hypertriglyceridemia is also observed, resulting from a decreased rate of triglyceride (TG) clearance from plasma due to diminished activity of hepatic TG lipase [6].

Lipocalin-2 (LCN-2), also called siderocalin, neutrophil gelatinase-associated lipocalin (NGAL), and uterocalin, is an adipokine recently classified, best described as a glycoprotein consisting of 198 amino acids. It is a member of the lipocalin superfamily, a group of proteins that circulate within the body and bind to and transport small, hydrophobic molecules, such as steroids, fatty acids, retinoids, prostaglandins, and hormones [7]. It is a 25-kDa protein that is associated with the body's inflammatory response and is involved in many of the body's systems and disorder processes, such as inflammation, infection, chronic renal failure, metabolism, and the growth and development of tumors. In addition, it functions as an adipokine because it is produced in and secreted from adipocytes. LCN-2 functions with many other adipokines and transport proteins that facilitate the transport of small, lip-soluble molecules in the blood [8].

During obesity, the pro-inflammatory adipokines take part in the initiation of local and systemic inflammation and contribute to comorbidities associated with obesity [9]. In addition, increased synthesis of LCN-2 has been linked to both intestinal and metabolic inflammation, particularly in the context of obesity and associated disorders [10]. Therefore, any change in the thyroid function with alteration in the 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. It can also contribute to the pathogenesis of obesity; this interrelation that is observed between thyroid function and adipokines production may contribute to the metabolic consequences of thyroid diseases [11]. According to our knowledge and literature search, to date, no studies in Iraq have assessed serum LCN-2 levels in hypothyroidism with obesity; however, a very few studies exist which estimated the LCN-2 levels in obesity and subclinical hypothyroidism worldwide. In prior research, no statistically significant difference in serum LCN-2 levels was identified between individuals with subclinical hypothyroidism and healthy control participants. While a positive correlation was established between serum LCN-2 levels and BMI [12].

The current study focused on the Iraqi cohort to fill an important regional data gap. Although a few similar studies have been conducted globally, evidence from Middle Eastern populations remains limited. Therefore, the study aims to elucidate the relationship between the LCN-2 levels and obesity, with and without hypothyroidism, as well as to explore the diagnostic accuracy of its level as a potential biomarker for Iraqi women with these conditions.

2. Materials and Methods

2.1 Subjects

A comparative cross-sectional study included a total of 140 Iraqi women aged between 18 and 45 years were enrolled in this study. The women were divided into four groups, each comprising 35 women, as follows:

- 1- Group (H1) is composed of women with obesity.
- 2- Group (H2) included women with newly diagnosed hypothyroidism.
- 3- Group (H3) consisted of women with newly diagnosed hypothyroidism and obesity.
- 4- Group (C) consisted of healthy women without either hypothyroidism or obesity, and served as a control group.

All participants were recruited through a convenience sampling strategy from Baghdad Medical City in Baghdad, Iraq, and diagnoses were made by specialist physicians during the period from September 2024 to January 2025, based on voluntary participation and fulfilment of predefined inclusion and exclusion criteria. A questionnaire was utilized to gather the medical history and personal information of each participant.

2.2 Sample size

The sample size required for the study was calculated through a power analysis by using G*Power software. The minimum sample size included in the study was 35 subjects showed 95% power.

2.3 Ethical clearance

The study received approval from the Ethical Committee of the College of Science at the University of Baghdad (Ref. CSEC/1024/0068 on October 6, 2024), and verbal consent was obtained from all participants.

2.4 Exclusion criteria

The study excluded women who had undergone a thyroidectomy, malignancies, pregnant individuals, smokers, and participants with acute or chronic inflammatory diseases. Additionally, individuals with a history of medication use, including medications for thyroid disorders and those affecting inflammation, were also excluded from the research to minimize confounding. These exclusions were intended to enhance internal validity and isolate the specific effects of the studied variables.

2.5 Blood samples

Blood samples were collected from each participant in the early morning (7:00-10:00 am) after an overnight fast (10-12 hours) and divided into two separate tubes: the first portion was transferred to EDTA tubes for the analysis of HbA1c, while the second portion was placed in a gel tube and allowed to clot at room temperature for 10 minutes. Then, the tube was centrifuged to separate serum at 3000 rpm for 10 minutes, and the serum aliquots were stored at - 20°C for a maximum of 2 months until analysis and thawed only once before analysis, to ensure sample integrity.

2.6 Laboratory assays

The BMI is calculated by dividing the weight (Kg) by the height squared (m^2) [13]. Fasting blood glucose (FBG) levels were assessed utilizing a glucose kit provided by Linear Company (Linear Chemicals S.L.U., Spain). Hemoglobin A1c (HbA1c) levels were quantified via Fluorescence Immunoassay (FIA) utilizing an automated BIOBASE analyzer (China). The level of thyroid hormones (Thyroid Stimulating Hormone (TSH), Thyroxine (T4) and T3) was evaluated by using the FIA technique (Fine care, China). Serum

concentrations of total cholesterol (TC), triglycerides (TG), and high-density lipoprotein (HDL) were measured using an enzymatic colorimetric method with a kit supplied by Bio Research, Germany. The Friedewald's equations were employed to calculate LDL level, which is equal to $[TC - HDL - (TG/5)]$, and very low-density lipoprotein (VLDL) level, which is equal to $(TG/5)$ [14]. The atherogenic index of plasma (AIP) was calculated from the equation $[AIP = \text{Log}_{10} (TG / HDL)]$. The AIP values are associated with cardiovascular risk, -0.3 to 0.1 with low risk, 0.1 to 0.24 with moderate risk and above 0.24 with high risk [15]. To calculate non-HDL cholesterol, HDL was subtracted from total cholesterol as follows: Non-HDL Cholesterol = TC – HDL [16].

The serum LCN-2 levels were determined using a sandwich enzyme-linked immunosorbent assay (ELISA) kit (Fine test company, China; Catalog no. EH0012) with a detection range of 0.313 – 20 ng/ml and a sensitivity (0.188 ng/ml). According to the manufacturer's validation data, the intra-assay coefficient of variation (CV) was 3-7%, and the inter-assay CV was 5-10%. All samples were conducted in duplicate, the calibration curve was generated using a six-point standard curve ($R^2 > 0.98$) and the mean optical density values were used for analysis to minimize random error. No cross-reactivity with related proteins was reported by the manufacturer.

2.6 Statistical Analysis

The data were analysed statistically using a statistical software package (SPSS program version 26). Normal distribution was confirmed across all groups, warranting the use of parametric statistical methods. For comparison, one-way analysis of variances (ANOVA) followed by post-Hoc Tukey's (HSD) test were used to examine the differences between groups. A significance level of $p < 0.05$ indicates that the observed differences are statistically significant, and $p \geq 0.05$ indicates no significant difference. The correlation between LCN-2 and other parameters was performed by Pearson correlation analysis. The optimal specificity and sensitivity of a diagnostic test can be determined through the application of the receiver operating characteristic (ROC) curve. Results are expressed as mean $\pm$ standard deviation (SD).

3. Results:

3.1 Demographic data and glycemic indicators

As indicated in Table 1, age did not differ significantly among the four study groups ($p \geq 0.05$). Conversely, BMI values (Kg/m^2) were substantially higher in the H1 (33.46 ± 3.00) and H3 (32.70 ± 2.27) groups compared to both the control (24.80 ± 2.28) and H2 (24.25 ± 1.92) cohorts (Figure 1). Furthermore, the findings indicated that the H3 group exhibited significantly higher levels of FBG (mg/dl) and HbA1c (%) when compared to C, H1 and H2 groups (Table 1).

Table 1: The mean $\pm$ SD of Age, FBG (mg/dl) and HbA1c (%) levels in all study groups.

Variables	Groups (n=35)			
	C	H1	H2	H3
Age (years)	33.17 $\pm$ 7.77	33.89 $\pm$ 8.05	32.11 $\pm$ 7.73	33.69 $\pm$ 8.38
FBG (mg/dl)	93.86 $\pm$ 6.69	*95.29 $\pm$ 7.11 ^{c,d}	*100.20 $\pm$ 7.87 ^{a,b,d}	*109.59 $\pm$ 8.79 ^{a,b,c}
HbA1c (%)	4.87 $\pm$ 0.61	*5.14 $\pm$ 0.47 ^{a,d}	*4.90 $\pm$ 0.06 ^d	*5.74 $\pm$ 0.05 ^{a,b,c}
The data was expressed as mean $\pm$ SD. * $p < 0.05$ using ANOVA followed by post-Hoc Tukey's test ^a significant when compared with C, ^b significant when compared with H1, ^c significant when compared with H2, ^d significant when compared with H3				

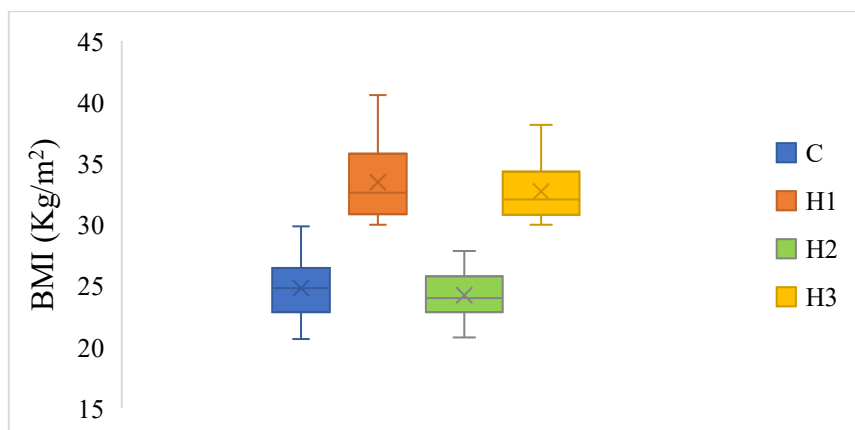


Figure 1: The mean±SD of BMI (kg/m²) in all study groups.

3.2 Thyroid Hormone Level

Table 2 lists the results of the thyroid hormone levels in the patients and controls. There was a significant ($p < 0.05$) increase in the TSH level in H2 and H3 groups as compared with H1 and C groups. There was a significant ($p < 0.05$) decrease in the levels of T3 and T4 in the patients' groups (H2 and H3) in comparison with the H1 and C groups.

Table 2: The mean±SD of thyroid hormone levels in all study groups.

Variables	Groups (n=35)				Normal values
	C	H1	H2	H3	
TSH (mIU/L)	2.01 ± 0.55	*1.67 ± 0.62 ^{c,d}	*11.88 ± 1.81 ^{a,b,d}	*14.91 ± 3.80 ^{a,b,c}	0.3-4.2
T3 (nmol/L)	1.87 ± 0.53	*2.01 ± 0.60 ^{c,d}	*0.79 ± 0.19 ^{a,b}	*0.72 ± 0.18 ^{a,b}	1.23-3.07
T4 (nmol/L)	88.3 ± 19.3	*94.2 ± 13.9 ^{c,d}	*50.6 ± 13.9 ^{a,b}	*53.9 ± 15.1 ^{a,b}	66-181

The data was expressed as mean±SD. * $p < 0.05$ using ANOVA followed by post-Hoc Tukey's test
^a significant when compared with C, ^b significant when compared with H1, ^c significant when compared with H2, ^d significant when compared with H3

3.3 Lipid Profile Level

As shown in Table 3 and Figure 2, TC, TG, LDL, VLDL, non-HDL, and AIP levels were significantly ($p < 0.05$) increased while HDL level showed a significant ($p < 0.05$) decrease in H3 group in comparison with the other study groups (C, H1 and H2).

Table 3: The mean±SD of lipid profile in all study groups.

Variables	Groups (n=35)			
	C	H1	H2	H3
TC (mg/dl)	114.7±18.0	*206.6±22.7 ^{a,d}	*212.5±16.6 ^{a,d}	*241.3±17.5 ^{a,b,c}
TG (mg/dl)	90.5±25.9	*200.8±40.6 ^a	*190.8±25.7 ^{a,d}	*213.7±22.4 ^{a,c}
HDL (mg/dl)	45.6±6.1	*37.9±8.5 ^{a,c,d}	*33.4±4.7 ^{a,b}	*31.1±3.7 ^{a,b}
LDL (mg/dl)	51.0±16.0	*128.6±24.7 ^{a,c,d}	*140.9±13.7 ^{a,b,d}	*167.4±15.6 ^{a,b,c}
VLDL (mg/dl)	18.1±5.2	*40.2±8.1 ^a	*38.2±5.1 ^{a,d}	*42.7±4.5 ^{a,c}
Non-HDL-C (mg/dl)	69.1±16.9	*168.7±24.0 ^{a,d}	*179.1±16.7 ^{a,d}	*210.2±17.4 ^{a,c,b}
AIP	0.103±0.05	*0.37±0.14 ^{a,c,d}	*0.40±0.08 ^{a,b,d}	*0.48±0.07 ^{a,b,c}

The data was expressed as mean±SD. * $p < 0.05$ using ANOVA followed by post-Hoc Tukey's test
^a significant when compared with C, ^b significant when compared with H1, ^c significant when compared with H2, ^d significant when compared with H3

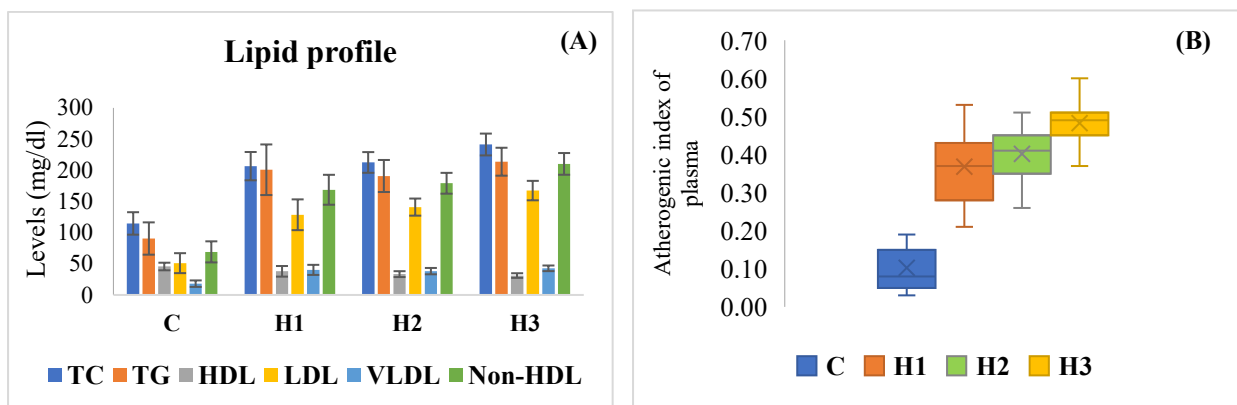


Figure 2: The mean $\pm$ SD of (A) lipid profile and (B) AIP in all study groups.

3.4 LCN-2 level and its correlation

In H1 and H3 groups, the results show that there is a significant increase ($p < 0.05$) in LCN-2 level (6.03 ± 1.17 and 7.38 ± 1.80 ng/ml, respectively) when compared with the C (3.51 ± 0.99 ng/ml) and H2 (4.20 ± 0.82 ng/ml) groups, while H3 group revealed the highest LCN-2 level in comparison with the other studied groups, as shown in Figure 3.

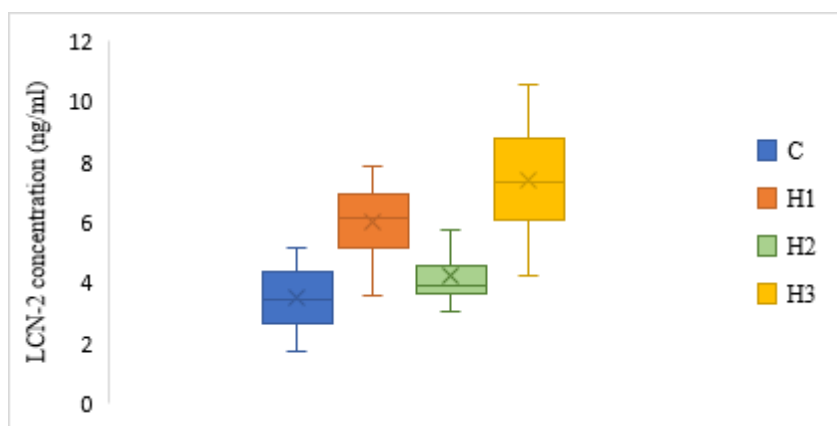


Figure 3: The mean $\pm$ SD of LCN-2 levels (ng/ml) in all study groups.

3.5 Pearson correlation of LCN-2 levels with other studied parameters

LCN-2 demonstrated significant moderate positive correlations with BMI across the groups, H1 group ($r=0.471$, 95% CI: 0.26–0.60, $p = 0.036$), H2 group ($r=0.427$, 95% CI: 0.29–0.67, $p = 0.036$) and H3 group ($r=0.533$, 95% CI: 0.24–0.74, $p = 0.047$). Additionally, LCN-2 exhibited significant moderate positive correlations with TSH in the H2 ($r=0.550$, 95% CI: 0.27–0.75, $p = 0.033$) and H3 ($r=0.607$, 95% CI: 0.44–0.78, $p = 0.038$) groups. While in H3 group, LCN-2 demonstrated a significant weak negative correlation with T3 ($r=-0.399$, 95% CI: -0.65 – -0.08, $p = 0.025$) and a significant moderate negative correlation with T4 ($r=-0.423$, 95% CI: -0.66 – -0.10, $p = 0.036$), as detailed in Table 4.

Table 4: Pearson correlation of LCN-2 levels (ng/ml) in relation to all parameters within the patient groups.

Variables (unit)	H1		H2		H3	
	r	p	r	p	r	p
BMI (Kg/m²)	0.471*	0.036	0.427*	0.036	0.533*	0.047
FBG (mg/dl)	-0.059	0.735	-0.020	0.909	0.037	0.835
HbA1c (%)	-0.191	0.271	-0.049	0.778	0.008	0.963
TSH (mIU/L)	-0.273	0.113	0.550*	0.033	0.607*	0.038
T3 (nmol/L)	0.165	0.345	0.254	0.141	-0.399*	0.025
T4 (nmol/L)	-0.009	0.957	-0.085	0.626	-0.423*	0.036
TC (mg/dl)	0.213	0.219	-0.206	0.235	-0.151	0.385
TG (mg/dl)	-0.065	0.711	-0.123	0.480	-0.124	0.478
HDL (mg/dl)	-0.048	0.785	0.050	0.773	-0.256	0.138
LDL (mg/dl)	0.225	0.194	-0.221	0.203	-0.074	0.672
VLDL (mg/dl)	-0.065	0.710	-0.123	0.480	-0.124	0.478
Non-HDL-C (mg/dl)	0.003	0.987	-0.107	0.541	0.125	0.475
AIP	0.218	0.207	-0.219	0.207	-0.098	0.574
* Correlation is significant at the p<0.05, r = Pearson correlation coefficient						

3.6 The ROC analysis

Receiver Operating Characteristic (ROC) curve analysis was employed to calculate the area under the curve (AUC) for assessing LCN-2's diagnostic utility in obesity and hypothyroidism cohorts, with results presented in Table 5 and Figure 4. The optimal sensitivity, specificity, and cut-off values were also determined. The AUC values for LCN-2 were found to be 0.943, 0.883, and 0.976 for the control vs. H1, H2, and H3 patient groups, respectively, indicating a strong ability to differentiate between control and patient groups. The corresponding cut-off values were established at > 4.36, > 3.67, and > 5.05 ng/ml, yielding sensitivities of 91.4%, 74.3%, and 91.4%, along with specificities of 77.1%, 91.4%, and 91.4% for the H1, H2, and H3 groups, respectively, as detailed in Table 5.

Table 5: The ROC of LCN-2 in the study groups.

Variable(s)	AUC (CIs)	Sensitivity % (CIs)	Specificity % (CIs)	Cut off value	Youden index
C vs. H1	0.943 (0.860 to 0.984)	91.4 (76.9-98.2)	77.1 (59.9-89.6)	> 4.36	0.743
C vs. H2	0.883 (0.784 to 0.947)	74.3 (56.7-87.5)	91.4 (76.9-98.2)	> 3.67	0.657
C vs. H3	0.976 (0.907 to 0.998)	91.4 (73.3-96.8)	91.4 (80.8-99.3)	> 5.05	0.829
Note: CIs = 95% Confidence Intervals C = control group, H1 = obesity group, H2 = hypothyroidism group, H3 = hypothyroidism with obesity group					

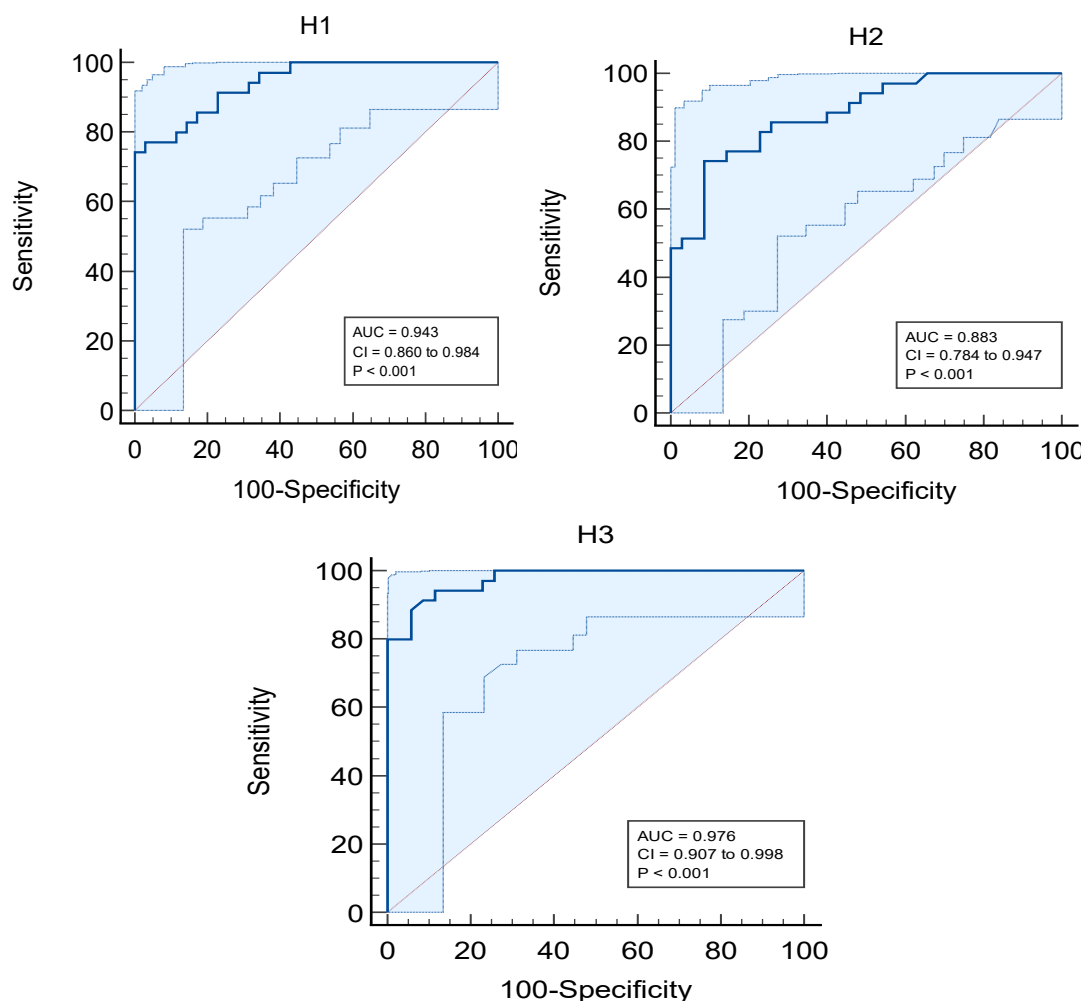


Figure 4: The ROC of LCN-2 in control vs. (H1) obesity, (H2) hypothyroidism and (H3) hypothyroidism with obesity.

4. Discussion:

Recent study findings indicate that patients with hypothyroidism have a normal weight, with a BMI of 24.25 ± 1.92 kg/m². In contrast, those with hypothyroidism who are classified as obese have a BMI of 32.70 ± 2.27 kg/m², which is significantly higher than the control group's BMI of 24.80 ± 2.28 kg/m². Hypothyroidism harms metabolism that affects lipid metabolism in fat tissue, and may lead to obesity and metabolic syndrome. The relationship between hypothyroidism and obesity is complex and may be bidirectional. Weight gain is a common symptom of overt hypothyroidism; while subclinical hypothyroid individuals may show associations with obesity. The observed BMI increase in the hypothyroidism with obesity group aligns with the known metabolic effects of hypothyroidism. The BMI is a commonly used tool to measure obesity and metabolic syndrome, which are themselves associated with higher cardiovascular risk [17]. Weight management is often more difficult in obese individuals, especially when combined with hypothyroidism, as individuals with hypothyroidism often struggle with weight gain that is challenging to manage [18]. Lipocalin-2 may be a novel regulator of food intake and energy homeostasis, and it may play a part in the onset of obesity and its complications, which acts as a satiety signal, promoting feelings of fullness and suppressing appetite, particularly in response to meals [19]. In addition, TSH and thyroid hormones significantly regulate the food intake and energy storage through the control and balance between lipogenesis and lipolysis, adipogenesis, and thermogenesis [20]. Our study reported that LCN-2 levels were highest in hypothyroidism

patients with obesity, followed by those with obesity alone, when compared to hypothyroidism and healthy individuals. Moreover, the LCN-2 levels are positively correlated with BMI in all patients' groups, and with TSH in hypothyroidism and hypothyroidism with obesity groups, while negatively correlated with T3 and T4 in the hypothyroidism with obesity group. This finding supports previous reports linking elevated LCN-2 levels with obesity related inflammation. The LCN-2 levels are often increased in obese individuals, and this elevation may be further increased in the presence of hypothyroidism. Previous studies have shown a positive correlation between LCN-2 levels and BMI, with higher levels in obese compared to lean individuals [21,22].

To the best of our knowledge and literature search, LCN-2 levels have never been assessed in hypothyroid patients with obesity. In the current study, LCN-2 levels are elevated in individuals with obesity, while those with hypothyroidism and obesity showed the highest level. So, based on these findings, LCN-2 may be a mechanistic link between obesity and hypothyroidism, as both conditions induce inflammation and lipid dysfunction. A state of hypothyroidism exacerbates adipose inflammation related to obesity, leading to increased LCN-2 levels. Thus, elevated LCN-2, in turn, promotes insulin resistance and cardiovascular risk may be seen in these patients. Several unmeasured potential confounders may have influenced the observed associations, including dietary intake and systemic inflammation, which are known to modulate circulating LCN-2 concentrations, potentially confounding its link with metabolic markers. Similarly, insulin resistance and hormonal status, especially the menopausal state in women, may independently affect both glycemic indices and LCN-2 [23]. Although these variables were not included in the present study, acknowledging their potential impact underscores the need for cautious interpretation of our findings and highlights the importance of adjusting for such variables in future studies.

Elevated levels of LCN-2 were indeed seen. However, it should be noted that LCN-2, in spite of having elevated levels linked to hypothyroidism and obesity, is a protein that can be influenced by a diverse range of factors, whether physiological or pathological. In addition to having a correlation with hypothyroidism and obesity, LCN-2, which is known as an acute-phase protein, can be known to have increased levels due to systemic inflammation, infections, and stress. Furthermore, under conditions of insulin resistance and obesity, LCN-2 is predominantly secreted by adipose tissues [24]. For women with hypothyroidism and obesity, a higher LCN-2 level can be justified due to the impact of inflammatory and metabolic dysregulation. Obesity is linked with the dysregulation of the adipose tissue, bringing about an inflammation of a chronic and low graded state, and triggering the over-secretion of inflammatory factors, in this case the pro-inflammatory adipokine LCN-2 [23]. In the case of hypothyroidism, there is a direct contribution to the changes which occur during lipid metabolism, the inflammation on the system, as well as the resistance to insulin, which can be responsible to even further increase LCN-2. The combination of these two factors appears to strengthen the inflammatory signals and secretion of adipocyte LCN-2, which causes increased levels in the circulation more than either one of the conditions would increase on their own [25], which may further stimulate production of LCN-2. The convergence of these two conditions may amplify inflammatory signalling pathways and adipocyte-derived LCN-2 secretion, resulting in higher circulating levels than either condition alone. This biological plausibility supports the LcN-2 potential role as an integrated biomarker reflecting both metabolic and endocrine disturbances in this population. Therefore, the observed increase in LCN-2 may reflect a combination of these overlapping pathways rather than a disease-specific effect, underscoring the need for cautious interpretation and further mechanistic studies.

In the present research, the hypothyroidism with obesity exhibited significantly elevated levels of TC, TG, LDL, and VLDL compared to the other groups, while their serum HDL level was lower. A previous study also found that obese individuals with hypothyroidism had notably higher levels of all lipid markers except for HDL, which was lower compared to healthy controls [26]. In addition, Al-Hakeim reported that there was a significant decrease in HDL and a significant increase in serum TC and LDL in hypothyroid patients as compared with the control group [27], which is in agreement with the current findings. The thyroid gland plays an important role in lipid metabolism because thyroid hormones modulate cholesterol production, transformation and clearance. On the other hand, Jouad and Al-Shammaree found significantly higher TC, TG and LDL levels in hypothyroidism patients when compared with the control group, while HDL showed no significant difference [28]. Our study also showed that AIP and non-HDL cholesterol were elevated in participants with obesity and hypothyroidism (with and without obesity) compared to normal controls. Interestingly, these markers are considered a reliable surrogate and an excellent predictor of cardiovascular risk in comparison to traditional lipid parameters [29]. The AIP is a lipid profile marker that indicates dyslipidemia, and its levels are higher in individuals with obesity. Particularly when thyroid autoimmunity is absent, a high AIP is related to a high risk of hypothyroidism, indicating that metabolic problems linked to obesity may be a factor in thyroid dysfunction. A recent study reported that women with hypothyroidism showed a significantly higher AIP (0.35 ± 0.2) compared to the control group (0.20 ± 0.08) [30], which is in agreement with our findings. Recently, Khan *et al.* found that non-HDL-cholesterol was significantly elevated in hypothyroidism cases (152.36 ± 24.42 mg/dl) as compared to controls (75.86 ± 24.42 mg/dl) [31]. This finding was in line with our results. Hypothyroidism affects the body's overall metabolic activities, which is strongly linked with hyperlipidemia and hyperglycemia. The risk of cardiometabolic disease rises when epicardial adipose tissue accumulates. Patients with hypothyroidism had significantly higher levels of epicardial adipose tissue, which raised risk of cardiometabolic risk [32]. Thus, the lipid abnormalities seem to be the connecting link between hypothyroidism and cardiometabolic risk. As the lipid abnormalities increased with obesity, which leads to an increased risk of cardiovascular disease among patients with hypothyroidism and obesity. Currently, there are limited studies on the impact of AIP and non-HDL cholesterol on thyroid function, especially with obesity, but thyroid dysfunction can lead to complex bidirectional changes in lipid metabolism. Therefore, the current results may suggest that obese and hypothyroid patients (with and without obesity) are at high risk of cardiovascular diseases, and regular monitoring for dyslipidemia is very important to start early treatment and advise them to change their lifestyle. In this study, women with hypothyroidism and obesity exhibited higher FBG and HbA1c levels compared to the control group, but still within normal values. This may suggest a link between hypothyroidism, obesity, and increased blood glucose levels, highlighting the importance of monitoring blood glucose in these individuals. Our finding aligns with previous research that also reported a significant HbA1c increase in obese and hypothyroid individuals with obesity than in controls [26]. Although the observed difference in HbA1c levels between groups was statistically significant, the absolute change was modest and may not represent a clinically meaningful effect. This finding likely reflects the sample size and low intra-group variability, which can yield statistical significance even for minor biological differences. In this research, women with diabetes were not included.

According to the ROC curve, our results indicate that the AUC for LCN-2 was significant, with p below 0.05. Lipocalin-2 showed an excellent diagnostic performance for predicting obesity and hypothyroidism with obesity women patients compared to the control group

(AUC = 0.943 and 0.976, respectively), while it showed a good diagnostic performance for predicting hypothyroidism (without obesity) in women patients compared to the control group (AUC = 0.883). Previous studies have estimated LCN-2 as a biomarker in obesity and metabolic disorders by performing ROC curve analysis for such disorders. For instance, in the case of obese women, serum LCN-2 demonstrated diagnostic performance for distinguishing between impaired glucose intolerance and type 2 diabetes mellitus, with the best cut-off value (80.5 ng/ml) [33]. In non-alcoholic fatty liver disease and non-alcoholic steatohepatitis, LCN-2 reached very high diagnostic performance (AUC = 0.987) using a cut-off value of 49 ng/ml [34]. Conversely, evidence in thyroid disease is limited, especially in hypothyroidism. Recent research reported ROC performance with a cut-off of 59 pg/ml in hyperthyroidism [11]. In addition, compared with other biomarkers reported in the literature, such as leptin (AUC = 0.95) and adiponectin (AUC = 0.93) in obese individuals with metabolic syndrome [35], LCN-2 shows comparable or slightly superior discriminatory capacity. However, as our sample size is limited, these comparisons should be interpreted cautiously. The present analysis underscores the promising biomarker potential of LCN-2 in obesity and hypothyroidism, while concurrently emphasizing the necessity for further validation in expanded, independent cohorts.

In future, further studies were needed to track LCN-2 before/after treatment for hypothyroidism and/or obesity, as well as investigate the LCN-2 relationship with specific obesity/hypothyroidism complications. In addition, mechanistic studies are required to explore the biological pathways linking LCN-2, thyroid dysfunction, and adiposity. Validation of the diagnostic performance (AUC) in larger, more diverse populations.

Study limitations

There are some limitations in this study that should be considered when we interpret our findings. A cross-sectional design does not allow assuming causality links between LCN-2 and the development of obesity and hypothyroidism. The longitudinal studies would also be helpful to clarify and investigate the temporal and mechanistic relationships underlying these associations. Also, the limited sample size (number of participants) and the lack of free T3/T4 measurements among the main studied parameters.

Conclusion

Hypothyroidism patients with obesity have a significantly higher level of LCN-2 compared to the obese and healthy controls. The LCN-2 increase might be linked with elevation of TSH in hypothyroidism patients, which is positively correlated to each other in this study, emphasizing the importance of LCN-2 role in the pathogenesis of hypothyroidism. Our findings suggest that elevated serum LCN-2 levels in obese women with hypothyroidism may have diagnostic implications as a potential biomarker. However, due to the study limitations, further large-scale, longitudinal studies are necessary to confirm its clinical utility.

Conflict of Interest

The authors declare there was no conflict of interest.

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