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The relationships between apelin, vaspin and thyroid hormone levels in obese diabetic and non-diabetic women

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Abstract

Apelin and vaspin modulate thyroid function. Furthermore, they are connected to particular components of chemical elements. Increased apelin and vaspin in diabetic women can have a negative impact on their thyroid function. The aim of the study was to understand the relationship between thyroid hormones and adipokine as a way to find a solution to the problem of obesity or its complications. Between October 1, 2022, and February 2, 2023, the case-control study included a total of 150 women, 100 obese women as the case group (50 obese and diabetic, 50 obese without diabetic), and 50 healthy women as the control group. They visited Al-Habbobi and Al-Nasiriyia teaching hospitals. Vaspin and apelin were measured using the enzyme-linked immunosorbent assay (ELISA), whereas C-Peptide was assessed using the electrochemiluminescence immunoassay (ECLIA) for thyroid hormone (FT3, FT4, and TSH). The measurement of fasting blood sugar (FBS) and haemoglobinA1C (HBA1C) was conducted using colorimetric and fluorescence immunoassay (FIA), respectively. In the results, in obese diabetics, vaspin is significantly lower than in controls. Although there is no significant difference in apelin levels between groups (0.34± 0.08 vs. 0.32± 0.11, P = 0,09), Vaspin and apelin tests show no significant difference between obese non-diabetics and controls. FT3 and TSH levels are significantly higher in obese diabetics and non-diabetics than in the control group. While FT4 dropped significantly between groups, in obese diabetics, FT3 and TSH levels are significantly higher than in obese non-diabetics. Obese diabetics had a significantly lower decrease in vaspin and apelin levels than obese non-diabetic patients. In conclusion, the decrease in FT4 across all groups and vaspin levels in obesity and diabetes suggest that vaspin is involved in thyroid hormone metabolism. Despite lower thyroid hormone levels, apelin levels were not statistically different. This suggests that the thyroid gland controls fat levels and metabolism.

Keywords: adipocytokines, obesity, apelin, vaspin, biomarkers, type 2 diabetes Mellitus, hypothyroidism

1. Introduction

Obesity refers to the abnormal or excessive buildup of adipose tissue or fat in the body. It increases the likelihood of developing hypertension, hyperlipidemia, diabetes, and cardiovascular disease. The state of public health has deteriorated during the past 50 years. There are multiple underlying factors that contribute to obesity and its associated health issues. In addition to smoking, this constitutes the second most prevalent cause of preventable death. The management of obesity necessitates a comprehensive approach and may need lifelong commitment. Reducing body weight by five to ten percent can have positive benefits on an individual's overall health and well-being, and economy of both individuals and the nation (1, 2). Body mass index (BMI) measurement is a common screening tool for obesity. To determine the body mass index (BMI), divide the weight in kilograms by the square of the height in meters. The BMI is between the range of 30 to 34.9 kg/m2, which is the definition of obesity (3, 4). An evident correlation exists between obesity and the surplus of body weight with type 2 diabetes mellitus. Individuals diagnosed with type 2 diabetes mellitus (T2DM) should follow the obesity management guidelines provided by the Obesity Association of America and the American Diabetes Association. The criteria listed above include pharmaceutical therapies, lifestyle modifications, and surgical indications. In 2016, the organizers of the Second Diabetes Surgery Summit created a treatment algorithm specifically designed for patients suffering from type 2 diabetes mellitus (T2DM) and obesity who are undergoing metabolic and bariatric surgery (5, 6). There is a strong correlation between body composition and thyroid hormones. Thyroid hormones control the basic rate of metabolism, the production of heat, and have a significant impact on the breakdown of fats and sugars, as well as on appetite and the burning of fat. Thyroid dysfunction is linked to alterations in body weight and composition, body

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temperature, and overall energy expenditure, both at rest and in total, regardless of physical activity (7). Hypothyroidism is associated with decreased thermogenesis and metabolic rate, as well as a positive correlation with a higher body mass index (BMI) and a higher prevalence of obesity (8). Clinical evidence indicates that even mild thyroid dysfunction, specifically subclinical hypothyroidism, is associated with substantial alterations in body weight and serves as a risk factor for overweight and obesity. Nevertheless, this topic still lacks definitive conclusions. It has been observed that even slight changes in serum TSH levels resulting from minor adjustments in L-T4 dosage during replacement therapy have a significant impact on the resting energy expenditure (REE) in patients with hypothyroidism (9). Apelin is classified as an adipokine, a peptide that occurs naturally. It carries out its function by attaching to the apelin receptor (APJ) receptor. Apelin's presence signifies its active involvement in numerous functions, including blood pressure regulation, maintenance of fluid balance, control of myocardial contraction, and energy metabolism. Additionally, it plays a role in disease mechanisms such as heart failure, obesity, and diabetes (10). Vaspin, alternatively referred to as serpin A12, was originally identified as an adipokine. Leptin is predominantly secreted by visceral adipose tissue in Otsuka Long Evans Tokushima adipose tissue (OLETF) and is employed for investigating obesity and type 2 diabetes. It has been observed that individuals with obesity, insulin resistance, and type 2 diabetes (T2DM) tend to have higher levels of vaspin in their blood and increased vaspin gene expression in their adipose tissue. Nevertheless, the precise mechanisms by which vaspin secretion may be associated with the decline of glucose metabolism and insulin sensitivity remain incompletely comprehended. Food intake affects the diurnal variation in vaspin serum concentrations. Vaspin is additionally present in the skin, hypothalamus, pancreatic islets, and stomach. The administration of vaspin to obese mice enhances their glucose tolerance and insulin sensitivity and decreases their food intake (11). The aim of this research was to evaluate the levels of vaspin, apelin, and thyroid hormones that might be in a relationship with obese, diabetic, and non-diabetic women.

2. Materials and methods

A case-control study, where the study included collecting 150 samples from women, including 100 samples from women suffering from obesity and diabetes as a case group (50 obese and diabetic, 50 obese without diabetic), and 50 healthy women with normal weight as a control group. The average age of the study participants was 35 years old. A delegation visited Al-Habbobi and Al-Nasiriyia Teaching Hospitals. The patients were examined by doctors at Al-Habbobi Teaching Hospital and Al-Nasiriyia Teaching Hospitals for the period between October 1, 2022, and February 10, 2023. The patient's weight and height were used to calculate the body mass index (BMI 18.5-24.9 is considered normal, while BMI 30 or more is considered obesity). Men and pregnant women or those under 30 years of age were excluded, and thyroid diseases and immune diseases were excluded. Women taking diabetes or obesity treatment were also excluded from the samples. The samples were included in the research according to the inclusion criteria, and the best 100 samples were selected according to the inclusion criteria. Collect blood samples to determine serum levels of vaspin, apelin, thyroid hormones (TSH, FT3, FT4), and glucose profiles (FBS, HBA1C, and C-peptide). Each patient and control subject had 5 ml of blood drawn. 2 ml in an EDTA tube within 30 minutes to measure HBA1C. 3 ml of blood was placed in a gel tube and left for 30 minutes for the purpose of coagulation. The serum was acquired through the process of centrifugation, where the vials were spun at a speed of 3000 revolutions per minute for a duration of 15 minutes. Serum is isolated and stored at -20 degrees Celsius until required. Sunlog instructed the use of an enzyme-linked immunosorbent assay (ELISA) to quantify vaspin and apelin. The electrochemiluminescence immunoassay (ECLIA) kits used in the immunoassay tests for FT3, FT4, TSH, and C. peptide can be used with immunoassay analyzers like the Cobas E-411 from Roche, Germany. The HBA1C test is carried out with the AFIAS-6 instrument and fluorescence immunoassay (FIA), as described in the Bodytech, S. Korea, operational manual. FBS is performed using a spectrophotometer and the colorimetric method, as described in the BIOLABO, France, operational manual.

2.1. Statistical Analysis

The data were stated as means ± standard deviation (SD). Differences between group means were tested by a t-test and a chi-square test. All statistical analyses were performed using SPSS for Windows (version 26, USA). The result was statistically significant at $P \leq 0.05$.

3. Results

3.1. Vaspin and Apelin levels between control and obese diabetic, Obese Non diabetic patient

The results show the levels of Vaspin and Apelin in the control and diabetic-obese groups. It showed a high significant decrease (P<0.001) in the levels of serum vaspin in obese diabetic patients as compared to control, while there is a non-significant difference in the levels of apelin in both groups (P = 0.09). The findings indicates that there is no substantial difference between vaspin and apelin (P = 0.13 and 0.14, respectively) in the obese non diabetic group when compared to the healthy control group (Table 1 and Fig. 1).

Table 1. Adipocytokine (Vaspin and Apelin) levels between control and obese diabetic, obese non-diabetic patient

Parameters	Control mean±SD	Obese Diabetic mean±SD	P value	Obese non-Diabetic mean±SD	P value
Vaspin (pg/ml)	0.25± 0.08	0.18± 0.05	**<0.001**	0.25± 0.10	0.13
Apelin (pg/ml)	0.34± 0.08	0.32± 0.11	0.09	0.34± 0.09	0.14

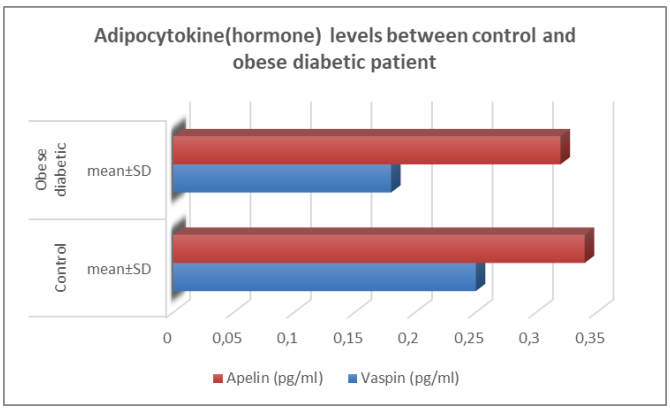

Fig. 1. (A). Adipocytokine(hormone) levels between control and obese diabetic patient

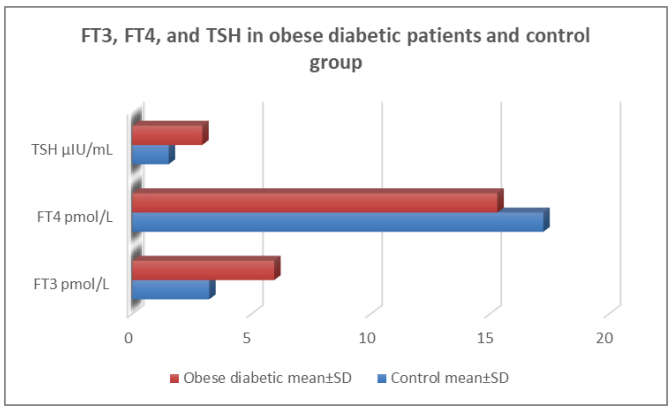

Fig. 2. (A). Thyroid hormone levels in obese diabetic patients and control group

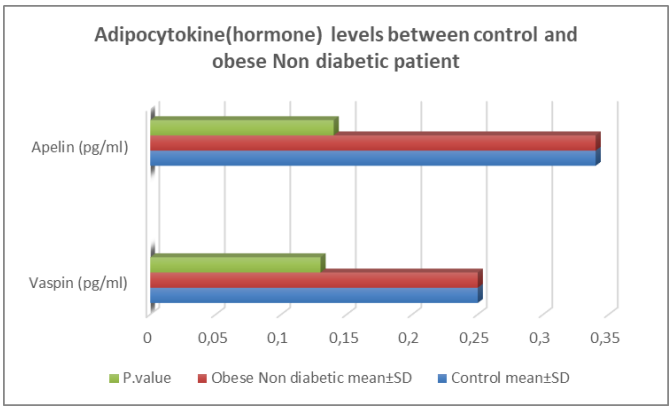

Fig. 1. (B) Adipocytokine(hormone) levels between control and obese Non diabetic patient

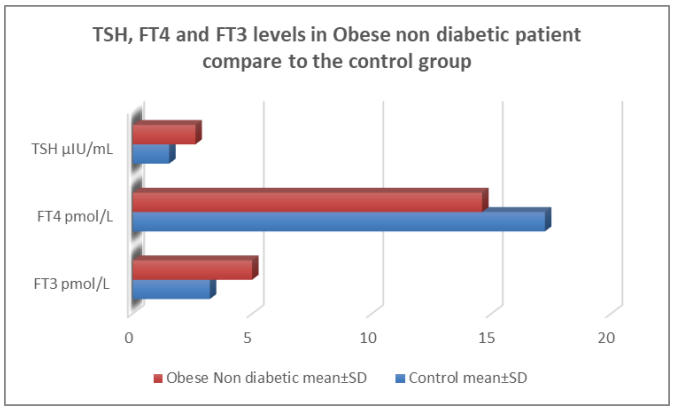

Fig. 2. (B) TSH, FT4 and FT3 levels in Obese non diabetic patient compare to the control group

3.2. Comparison between hormone levels (thyroid hormones) in patients (obese diabetic, obese non diabetic) and the control group

The results reveal the concentrations of FT3, FT4, and TSH in both the control and obese-diabetic groups. A significant increase (P<0.001) is detected in the concentrations of FT3 and TSH, whereas a significant decrease (P<0.001) is observed in the levels of FT4, compared to the healthy group consisting of obese diabetes individuals. Additionally, the control and obese non-diabetic groups were evaluated for their FT3, FT4, and TSH levels. FT3 and TSH levels shows a high and significant elevation in the obese non-diabetic group (P<0.001). On the other hand, the levels of FT4 in obese non-diabetics showed a significant decrease (P<0.001) (Table 2 and Fig. 2).

Table 2. Levels of thyroid hormones in the two groups included in the study (Obese diabetic group, Obese non diabetic and Control group)

Parameters	Control mean±SD	Obese Diabetic mean±SD	P value	Obese non-Diabetic mean±SD	P value
FT3 pmol/L	3.22±0.26	5.95±0.36	**<0.001**	4.99±0.36	**<0.001**
FT4 pmol/L	17.24±0.42	15.31±0.46	**<0.001**	14.61±0.37	**<0.001**
TSH µIU/mL	1.52±0.51	2.93±0.07	**<0.001**	2.62±0.11	**<0.001**

3.3. Comparison between adipocytokine and thyroid hormone levels between an obese diabetic group and a non-diabetic obese group

The findings indicate that obese individuals with diabetes exhibit reduced levels of vaspin and apelin compared to obese individuals without diabetes (P = 0.001, 0.04). The findings indicate a notable elevation in TSH, FT4, and FT3 concentrations among obese individuals with diabetes in comparison to obese individuals without diabetes (P<0.05) (Table 3 and Fig. 3).

Table 3. Differences of the adipocytokine and thyroid hormone levels between obese diabetic and obese non diabetic patient

Parameters	Obese Diabetic mean±SD	Obese non-Diabetic mean±SD	P value
Vaspin (pg/ml)	0.25± 0.10	0.18± 0.05	**<0.001**
Apelin (pg/ml)	0.34± 0.09	0.32± 0.11	**0.04**
TSH	2.62±0.11	2.93±0.07	**<0.05**
FT3	4.99±0.36	5.95±0.36	**<0.05**
FT4	14.61±0.37	15.31±0.46	**<0.05**

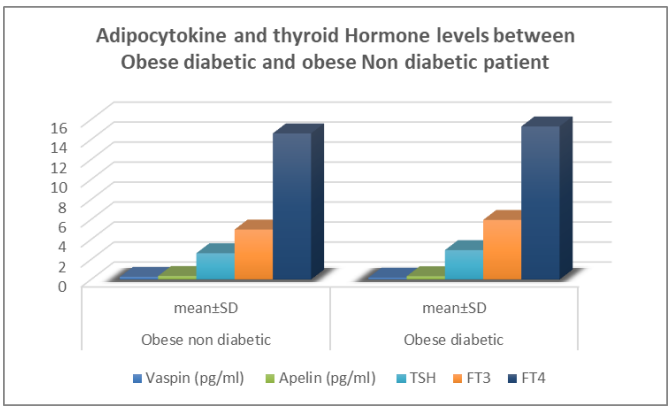

Fig. 3. Adipocytokine and thyroid hormone levels between obese diabetic and obese non diabetic patient

3.4. Differences of the FBS, HbA1C and C-Peptide levels between control and obese diabetic, obese non diabetic patient.

The results reveal that, when compared to the control group, obese diabetic patients had significantly higher levels of HBA1C, C. peptide, and FBS (P = <0.001). The results indicate that there is no significant difference in HBA1C and C peptide levels between obese non-diabetic patients and the control group (P = 0.58, 0.08), respectively. There was a notable rise in fasting blood sugar (FBS) levels among obese non-diabetic patients compared to the control group (P = <0.01).

Table 4. Differences of the FBS, HbA1C and C. Peptide levels between control and obese diabetic, obese non diabetic patient

Parameters	Control mean±SD	Obese Diabetic mean±SD	P value	Obese non-Diabetic mean±SD	P value
HBA1C	5.0±0.47	8.22±0.95	**<0.001**	4.94±0.32	0.58
C. peptide	0.97±0.35	2.71±0.42	**<0.001**	0.83±0.52	**0.08**
FBS	91.66±8.85	175.38±37.46	**<0.001**	98.99±14.09	**<0.01**

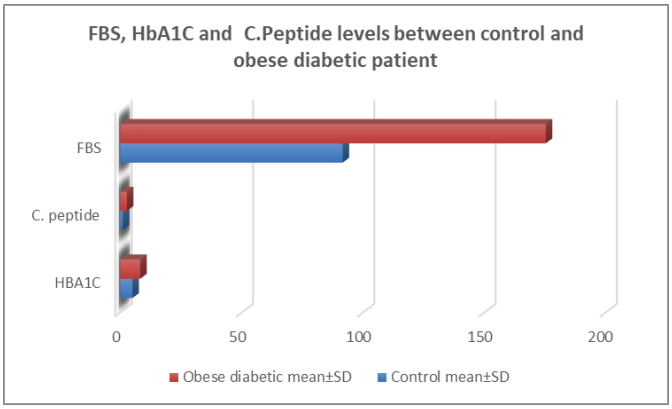

Fig. 4. (A) FBS, HbA1C and C. Peptide levels between control and obese diabetic patient

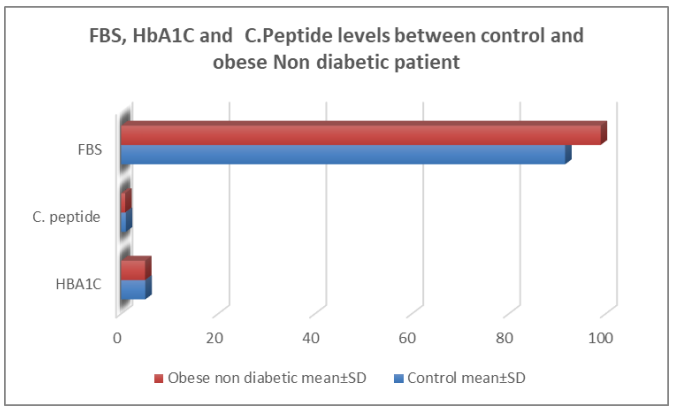

Fig. 4. (B) FBS, HbA1C and C. Peptide levels between control and obese non diabetic patient

4. Discussion

This study is consistent with Soriguer et al. (2009), whose results showed a decrease in apelin levels in the obese diabetic group when compared to the control group, while he also concluded that there was no statistical significance in the levels of vaspin between the two groups (12). Apelin levels increase in people with obesity and diabetes. This is due to the increase in adipose tissue, which leads to increased gene expression of the hormone apelin, so its levels are high. Insulin resistance is a condition where the body does not respond adequately to insulin, leading to an increased release of apelin (APL). This compensatory mechanism aims to alleviate the strain on the pancreas and enhance insulin sensitivity. Nevertheless, in the event of a defect in the adipose tissue, an increased quantity of apelin is released as a result of the enlargement of the adipose tissue. The results of Erdem et al. (2008), research showed lower levels of apelin in the obese diabetic group compared to the control group (13). Apelin, a peptide hormone, regulates glucose metabolism and energy balance. Weighty diabetics have lower apelin levels than thin people. Multiple explanations exist for this phenomenon. Obesity and diabetes may reduce apelin synthesis and secretion from adipose tissue due to chronic inflammation and oxidative stress. Insulin resistance, common in obese and diabetic people, can also impair apelin signaling. Insulin, obesity, and diabetes medications can all affect apelin levels. Additional research is necessary to understand the underlying causes of the decreased apelin levels observed in individuals with obesity and diabetes (14). There is no statistical significance in the levels of apelin and vaspin when comparing the obese group with diabetes and those without diabetes; this result agrees with Cavallo et al. (2018) and Jian et al. (2014), (15, 16). Vaspin is one of the peptide hormones that has an important role in insulin sensitivity and glucose metabolism. Apelin and vaspin can affect obese and non-diabetic patients, and vaspin may not have a role in obese and non-diabetic patients due to a number of factors, including the lack of an important role for vaspin in glucose metabolism in addition to insulin sensitivity. In addition to the insufficient sample size for the purpose of detecting statistical significance, as we mentioned previously, apelin is a hormone that plays an important role in many

metabolic processes. The levels of apelin in obese and non-diabetic people are not noticeable due to a number of factors, such as individual variation, the percentage of visceral fat, and its location in the body, in addition to the use of many treatments that affect the levels of apelin. This result disagrees with (17). The basal and post-weight loss serum levels of apelin-13 in the obese group were significantly lower than those in the control group ($p<0.05$). Multiple factors can contribute to increased levels of apelin and vaspin in non-diabetic patients who are obese. 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 and vaspin (18). The TSH levels showed a significant increase in all groups compared to the control group ($P = 0.001$). This result agrees with Reinehr et al. (2008). Studies have demonstrated a negative association between free T4 (FT4) and body mass index (BMI), even when free thyroxine (FT4) levels are within the normal range. Nevertheless, there is a correlation between the accumulation of fat and decreased levels of free thyroxine (FT4), as well as increased levels of thyroid stimulating hormone (TSH) and free triiodothyronine (FT3), in individuals who are slightly overweight but have normal thyroid function. Changes in energy expenditure, which can be attributed to abnormal thyroid function and normal feedback control, can lead to increases in body mass index and weight (20). The causes of these thyroid function changes are currently unknown. According to one theory, an increased rate of conversion from T4 to T3 could be attributed to increased deiodinase activity. This is thought to serve as a defensive mechanism in obese people, slowing or stopping the progression of obesity by increasing energy expenditure (21). When fat cells release inflammatory cytokines like tumor necrosis factor alpha, interleukin-1, and interleukin-6, they stop the activity of iodide uptake and the expression of sodium/iodide symporter mRNA. Subsequent studies have failed to establish a link between the increase in TSH blood levels and a lack of iodine, or autoimmune thyroiditis (22). Adipocyte dysfunction is caused by obesity and lipodystrophy, leading to changes in adipocytokines and resulting in metabolic and energy-related disorders (23). Malfunctions in adipose tissue impact thyroid function and energy metabolism (24). Thyroid dysfunction impacts body weight, the process of generating heat in the body, and the breakdown of fat in adipose tissue. Hypothyroidism often leads to increased body weight, decreased body temperature, and a reduced metabolic rate. Nevertheless, hyperthyroidism leads to weight loss in spite of heightened appetite and metabolism. The majority of metabolic variations are attributed to alterations in adipose tissue. Body mass, temperature, weight, obesity, insulin resistance, glucose, and lipid metabolism are factors that affect thyroid hormones and adipocytokines. Additionally, they exert an influence on these metabolic processes. Thyroid-stimulating hormone (TSH) and receptors for thyroid hormones are present in adipose tissue, while receptors for apelin are located in the thyroid. 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 (25, 26). 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 (27). Obese women showed a negative correlation between TSH and adiponectin (ADPN) levels, while healthy persons with normal thyroid function showed a negative correlation between adiponectin and free thyroid hormones (28). A separate study found a clear association between serum resistin levels and FT3 and FT4, but not with TSH. Moreover, a connection was shown between effective treatment of hyperthyroidism and a reduction in resistin levels (29, 30). Apelin expression in adipose tissue is increased in rodent models of hyperinsulinemia-induced obesity, leading to higher levels of apelin in the bloodstream (14). Rats that have fasted exhibit a substantial decrease in Apelin expression. However, obese patients exhibited markedly elevated levels of apelin and insulin in their bloodstream (15). Insulin and apelin, both secreted by adipocytes, exhibit a robust correlation. Moreover, research conducted on rat models has demonstrated that obesity accompanied by hyperinsulinemia leads to elevated levels of apelin in the bloodstream and increased expression of apelin mRNA in adipocytes (31). The clinical interest lies in comprehending the correlation among thyroid gland function, insulin resistance, and obesity. Consequently, there is a significant focus on investigating adipokines as the mediator between these factors. Insufficient investigation has been carried out regarding the correlation between the thyroid gland and the manifestation of vaspin. Vaspin levels exhibited no significant variation among patients with overt hypothyroidism, subclinical hypothyroidism, and normal thyroid function. In addition, there was no observed association between vaspin and thyroid-stimulating hormone (TSH), T3, or T4 levels (32). However, it is important to note that the study was constrained by the small size of the sample. Moreover, specific research has indicated that individuals suffering from hypothyroidism exhibit a substantial elevation in vaspin levels in their circulatory system, while those with hyperthyroidism experience a significant reduction in vaspin levels compared to the control group (33, 34).

The observed discrepancies among studies may be attributed to the ethnicities of the patients. Polymorphism in genes is associated with the origin of populations and has the capacity to modify protein characteristics. There is a correlation between weight loss and decreased levels of vaspin and TSH in the bloodstream. Nevertheless, it remains uncertain whether the decline in TSH levels is attributed to vaspin due to

weight loss or if thyroid function directly impacts vaspin levels in the bloodstream. Further investigation is required to ascertain the expression and function of vaspin in the thyroid.

Ethical Statement

Verbal consent was obtained from all study participants, and an ethical consent form was signed by the participants. This study adhered to the ethical principles outlined in the Declaration of Helsinki (1964), which provides guidelines for conducting medical research with human beings. The investigation received ethical approval from the Department of Chemistry and Biochemistry's ethics and research committee. College of Medicine, Al-Nahrain University, Baghdad, Iraq. The Document number 645, dated 29/8/2022.

Conflict of interest

The authors declare that they have no competing interests.

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Authors' contributions

Concept: D.A.L., N.A.N., O.A.M., Design: D.A.L., N.A.N., O.A.M., Data Collection or Processing: D.A.L., N.A.N., O.A.M., Analysis or Interpretation: D.A.L., N.A.N., O.A.M., Literature Search: D.A.L., N.A.N., O.A.M., Writing: D.A.L., N.A.N., O.A.M.

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