Al-Rafidain J Med Sci. 2025;8(2 Special):S1-7.
DOI: https://doi.org/10.54133/ajms.v8i(2S).1362

Proceeding of the 6th International Scientific Conference Middle Technical University/ Baghdad 2024

AJMS
Online ISSN (2789-3219)

Research Article

Serum Levels of FABP4 and Fetuin-A as Potential Biomarkers in Thyroid Diseases: A Comparative Study

Burhan Talip Lafta[1], Suhad Hassan Aubaid[2]*, Ekhlas Saddam Falih[2]
[1]*Baghdad Karkh Health Directorate, Iraqi Ministry of Health, Baghdad, Iraq;* [2]*Department of Medical Laboratory Techniques, College of Health and Medical Technology, Middle Technical University, Baghdad, Iraq*
Received: 15 September 2024; Revised: 10 November 2024; Accepted: 17 December 2024

Abstract

Background: Fatty acid-binding protein 4 (FABP4) moves lipids inside cells. Fetuin-A is a liver-derived glycoprotein that prevents vascular calcification. Recent studies link higher serum levels of both proteins to metabolic syndrome, suggesting a risk for metabolic issues. ***Objectives***: To explore the roles of FABP4 and Fetuin-A as biomarkers in thyroid diseases. The outcomes of this research have important ramifications for both prevention and treatment methods. Approach: ***Methods***: For this specific research, a case-control study methodology was employed, comprising a newly diagnosed 120 thyroid disease patients. 30 healthy controls were age- and gender-matched to these patients. Using the enzyme-linked immunosorbent assay (ELISA) method, fetuin-A and FABP4 concentrations were assessed. ***Results***: Individuals with thyroid diseases showed significantly elevated levels of both biomarkers compared to the healthy control group (p<0.001). This observation was significant in terms of its sensitivity and specificity. Additionally, a solid correlation between FABP4 and fetuin-A was found, with a correlation coefficient of r=0.8199 and a significance of p=0.000. ***Conclusions***: Based on these findings, FABP4 and fetuin-A may be crucial in metabolic irregularities linked to thyroid dysfunction.

Keywords: Fatty acid-binding protein, Fetuin-A, Thyroid disease.

مستويات مصل FABP4 و Fetuin-A كمؤشرات حيوية محتملة في أمراض الغدة الدرقية: دراسة مقارنة

الخلاصة

الخلفية: يحرك البروتين المرتبط بالأحماض الدهنية 4 (FABP4) الدهون داخل الخلايا. Fetuin-A هو بروتين سكري مشتق من الكبد يمنع تكلس الأوعية الدموية. تربط الدراسات الحديثة بين ارتفاع مستويات المصل لكلا البروتينين ومتلازمة التمثيل الغذائي ، مما يشير إلى خطر الإصابة بمشاكل التمثيل الغذائي. **الأهداف**: استكشاف أدوار FABP4 و Fetuin-A كمؤشرات حيوية في أمراض الغدة الدرقية. نتائج هذا البحث لها تداعيات مهمة على كل من طرق الوقاية والعلاج. النهج: **الطرائق**: في هذا البحث المحدد ، تم استخدام منهجية دراسة الحالة والشواهد ، والتي تضم 120 مريضا بأمراض الغدة الدرقية تم تشخيصهم حديثا. تم مطابقة 30 ضابطا صحيا حسب العمر والجنس مع هؤلاء المرضى. باستخدام طريقة مقايسة الممتز المناعي المرتبط بالإنزيم (ELISA) ، تم تقييم تركيزات الفيتوين-A و FABP4. **النتائج**: أظهر الأفراد المصابون بأمراض الغدة الدرقية مستويات مرتفعة بشكل ملحوظ لكلا العلامتين الحيويتين مقارنة بالمجموعة الضابطة السليمة ($p<0.001$). كانت هذه الملاحظة مهمة من حيث حساسيتها وخصوصيتها. بالإضافة إلى ذلك ، تم العثور على ارتباط قوي بين *FABP4* و *fetuin-A* ، مع معامل ارتباط $r = 0.8199$ ودلالة $p = 0.000$. **الاستنتاجات**: بناء على هذه النتائج ، قد يكون FABP4 و fetuin-A حاسمين في المخالفات الأيضية المرتبطة بضعف الغدة الدرقية.

* ***Corresponding author***: Suhad H. Aubaid, Department of Medical Laboratory Techniques, College of Health and Medical Technology, Middle Technical University, Baghdad, Iraq; Email: alsuhad4@gmail.com
Article citation: Lafta BT, Aubaid SH, Falih ES. Serum Levels of FABP4 and Fetuin-A as Potential Biomarkers in Thyroid Diseases: A Comparative Study. *Al-Rafidain J Med Sci*. 2024;8(2 Special):S1-7. doi: https://doi.org/10.54133/ajms.v8i(2S).1362

INTRODUCTION

Adipokines are a large group of molecules expressed by adipose tissue. Molecules like fetuin-A are blood proteins that are made in the liver and secreted into the bloodstream. Hepatocytes are crucial in metabolism. Thyroid hormones affect adipose tissue's metabolic responses. Fatty acid binding protein 4 (FABP4) is a cytoplasmic fatty acid chaperone expressed primarily in adipocytes and myeloid cells and implicated in the development of insulin resistance and atherosclerosis. Key players of fetuin-A and FABP4 signify the interplay among adipose tissue, liver, and endocrine functions [1]. Beyond the influencing regular growth, maturation, and reproduction, thyroid hormones critically modulate energy use and the structure of the body [2]. Peretianu's global research indicates that midlife often witnesses a surge in thyroid issues, such as hyperthyroidism, hypothyroidism, thyroiditis, goiter, thyroid nodules, and even thyroid cancer [3]. A range of adipokines, including progranulin, monocyte chemoattractant protein-1 (MCP-1), resistin, chemerin, leptin, and FABP4, along with liver

proteins like fibroblast growth factor 21 (FGF21), growth differentiation factor 15 (GDF15) (mesencephalic astrocyte-derived neurotrophic factor (MANF)), and fetuin-A, associated with obesity-triggered concerns like dyslipidemia, metabolic imbalance, type 2 diabetes, and atherosclerosis risks [4]. There is mounting evidence positioning fetuin-A and FABP4 as potential indicators for heart-related issues and type 2 diabetes [5]. In addition, fetuin-A, an esteemed protein emanating from the liver's intricate laboratories, acts as a vigilant sentinel, warding off the undesirable accretion of calcium within the arterial conduits. By engaging with serum calcium and phosphorus, it enhances their solubility, preventing the formation of calcium crystals [6]. It is of utmost importance to note that attenuated concentrations of fetuin-A bear a poignant association with cardiovascular difficulties and the general specter of mortality in those suffering from end-stage renal disease (ESRD) [7]. Interestingly, elevated levels of fetuin-A signal hepatosteatosis and insulin resistance [8]. Additionally, fetuin-A acts as a forecasting biomarker for emerging type 2 diabetes, evidenced by the EPIC (Eukaryotic Pathogens Innovation Center) study where its levels forecasted the condition's onset over seven years [9]. Fatty acid binding protein 4, illustriously recognized as adipocyte FABP or the eminent adipocyte protein 2, reigns with distinction within adipocytes. However, endothelial cells and macrophages also produce significant amounts of FABP4. Functioning as a lipid chaperone, FABP4 modifies cell membranes and assists in transporting fatty acids intracellularly [10]. Recent findings associate FABP4 with diabetes and cardiovascular ailments. In individuals with metabolic syndrome, obesity, hypertension, and habits like smoking, aerobics, and alcohol intake, and conditions including dyslipidemia, cardiac issues, gestational diabetes, both types of diabetes, and renal failure, elevated blood FABP4 levels were observed [11]. Yet, the metabolic irregularities in thyroid disorders are only partially understood [12]. Proteins such as adipokines and hepatokines are considered bridges between thyroid function and metabolism, with FABP4 being extensively researched and fetuin-A also playing a role. However, the relationship of plasma fetuin-A and FABP4 levels to thyroid diseases remains ambiguous. Consequently, this study aims to elucidate the intricate relationship between thyroid functions and metabolic processes. While proteins like adipokines and hepatokines serve as connectors between these realms, the roles of FABP4 and fetuin-A have generated significant attention. The primary objectives are to discern the correlation between serum levels of FABP4 and fetuin-A and their relation to various thyroid conditions. Through this exploration, I hope to shed light on these biomarkers' significance, providing clarity to the currently ambiguous connections they have with thyroid disorders.

METHODS

Design of study

Between the temporal bounds of November 2022 and March 2023, this case-control inquiry was judiciously executed within the hallowed confines of the Specialized Center for Endocrinology and Diabetes, Baghdad, Iraq. The research involved a total of 150 participants divided into two groups. Thirty individuals, assessed to be in optimal health, comprised the control group. The other 120, diagnosed by expert consultant endocrinologists and corroborated with laboratory tests, had various thyroid-related conditions, including cancer, hypothyroidism, hyperthyroidism, and goiter. They were also on a stable medication regimen for a certain period before sample collection. Exclusion criteria included pregnancy, acute illness or inflammatory conditions, a history of other endocrine disorders, or previous thyroid surgeries.

Specimen collection, processing and assessments

For both FABP4 and fetuin-A measurements, disposable syringes were used to draw five milliliters of blood from each participant into gel disposable tubes. FABP4 Quantification: After collection, the whole blood was refrigerated at 4℃ overnight. The following day, it was centrifuged for 10 minutes at speeds of 3000 rpm to separate the serum. This serum supernatant was either tested immediately or stored at -20℃ for up to three months (if applicable). For the quantification of FABP4, we utilized the Human Fatty Acid Binding Protein (FBAP) sandwich ELISA Kit (My BioSource-USA, Cat No. MBS268011) [11] following manufacturer instructions. This kit is carefully made for accurately measuring levels of FABP in human serum, plasma, or cell culture fluid. It works well for both naturally occurring and man-made FABP. Fetuin-A Quantification: The whole blood sample was either left at room temperature for 2 hours or refrigerated at 2-8℃ overnight for serum preparation. After this, the sample was centrifuged for 20 minutes at approximately 1000xg, separating the supernatant, which was then immediately subjected to the assay. For this quantification, we employed the Human Fetuin-A sandwich ELISA Kit (My BioSource-USA, Cat No. MBS763509), suitable for quantitative detection of fetuin-A in serum, plasma, tissue homogenates, and other biological fluids [12]. Serum levels of TSH, T4, and T3 were assessed using AIA-PACK test cups. For TSH, a two-site immunoenzymometric assay was employed, while T4 levels were gauged through a competitive immunoassay. The T3 assessment followed a methodology consistent with the T4 procedure [12]. The Body Mass Index (BMI) was assessed using a specific formula derived from an individual's height and weight measurements.

Ethical consideration

The Iraqi Ministry of Health/Department of Medical Teaching City bestowed ethical sanction for this investigation, as manifested in their letter dated December 4, 2022, bearing the reference number

51158. Each participant, with full volition, rendered verbal affirmation to be a part of this study.

Statistical analysis

The SPSS-26 software (Statistical Packages for Social Sciences-version 25) was the chosen instrument for our data dissection, eloquently rendering data in terms of mean, SD, and percentage. We summoned Pearson correlation to elucidate the intricate relationships amongst groups, while the venerable independent sample t-test was tasked to probe the quantitative associations. A p-value, when it gracefully descends below 0.05, was deemed to bear statistical import. The esteemed ROC benchmarks [13] served as a guide for the delineation of cut-off values.

RESULTS

In Table 1, the basic characteristics of the research population are delineated by thyroid condition. The age (in years) for those with hypothyroidism, hyperthyroidism, thyroid cancer, thyroid goiter, and the control group was 41.17±13.03, 45.73±11.81, 45.83±12.29, 41.17±13.03, and 38.10±8.16, respectively. The p-value for age was 0.52, indicating no significant difference across the groups.

Table 1: The basic characteristics of the research population.

Variables	Hypothyroidism	Hyperthyroidism	Thyroid Cancer	Thyroid Goiter	Control	*p*-value (ANOVA)
Age (year)	41.17±13.03	45.73±11.81	45.83±12.29	41.17±13.03	38.10±8.16	0.52
BMI (kg/m^2)	31.48 ±5.12	24.17± 2.69	29.08±4.89	29.17±37.01	22.84±1.86	0.00
Total	30	30	30	30	30	

Values were expressed as mean±SD.

Concerning Body Mass Index (BMI), the mean values were 31.48±5.12 for hypothyroidism, 24.17±2.69 for hyperthyroidism, 29.08±4.89 for different stages of thyroid cancer, 29.17±37.01 for thyroid goiter (hypo- and hyperthyroidism), and 22.84±1.86 for the control group. The BMI showed a significant difference with a p-value of 0.000. Table 2 presents the serum levels of FABP4 across the studied groups. In comparison to the control group (9.96±5.34), patients with hyperthyroidism and hypothyroidism exhibited notably elevated mean concentrations of serum FABP4, registering values of 22.31±2.73 ng/ml and 21.41±2.66 ng/ml, respectively.

Table 2: Serum level of FABP4 according to studied groups

	Hyperthyroidism	Hypothyroidism	Thyroid Cancer	Thyroid Goiter	Control	*p*-value (ANOVA)
FABP4 (ng/ml)	22.31±2.73	21.41±2.66	32.54±5.68	15.20±6.28	9.96±5.34	0.001
p-value Bonferroni test	0.949		0.0001		0.0001	

In contrast, the mean concentrations for thyroid cancer and thyroid goiter were 32.54±5.68 ng/ml and 15.20±6.28 ng/ml, respectively. Statistical analysis revealed pronounced differences in serum FABP4 concentrations between the control group and the patients with the specified conditions, with a significance level of $p < 0.001$. Notably, the study established that elevated serum FABP4 levels were prevalent in patients with hyperthyroidism, hypothyroidism, thyroid cancer, and thyroid goiter, suggesting a marked influence on thyroid functionality. In Table 3, the diagnostic performance of FABP-4 in thyroid patients was assessed. For a cut-off point of 17.6 ng/ml, FABP-4 demonstrated a sensitivity of 100% and a specificity of 97%. The area under the receiver operating characteristic (AUROC) was found to be 1, indicating perfect diagnostic accuracy.

Table 3: Estimation of FABP-4 threshold, sensitivity, specificity and AUROC in thyroid patients

Parameters	Cut-off points	Sensitivity (%)	Specificity (%)	AUROC	*p*-value
FABP-4 (ng/ml)	17.6	100	97	1.0	0.000

The *p*-value associated with these findings was less than 0.000, signifying high statistical significance ($p < 0.05$). Table 4 presents the levels of Fetuin-A across different groups. The mean concentration of Fetuin-A for the hyperthyroidism group was 1.19±0.57 ng/ml, while for hypothyroidism it was 14.32±2.61 ng/ml. For those with thyroid cancer and thyroid goiter, the levels were 19.35±5.53 ng/ml and 11.85±2.30 ng/ml, respectively. In contrast, the control group had a mean concentration of 5.97±1.90 ng/ml.

Table 4: Comparative Analysis of serum fetuin-A levels among the investigated groups.

	Hyperthyroidism	Hypothyroidism	Thyroid Cancer	Thyroid Goiter	Control	*p*-value (ANOVA)
Fetuin-A (ng/ml)	1.19 ±0.57	14.32±2.61	19.35±5.53	11.85±2.3	5.97±1.9	0.000
p-value (*pot hoc*)	0.0001		0.0001		0.0001	

The analysis revealed that the mean serum concentrations of fetuin-A in patients with hyperthyroidism and hypothyroidism were significantly different. Similarly, significant differences were noted between the levels in the thyroid cancer and thyroid Goiter groups. Notably, the serum levels of fetuin-A in patients with thyroid disorders were markedly higher than in the healthy control group, with a significance level of $p < 0.001$. Table 5 demonstrates the diagnostic performance of Fetuin A in distinguishing thyroid disease. With a cut-off value of 8.5 ng/ml, Fetuin A achieved an AUROC of 1.0 ($p = 0.000$), reflecting a sensitivity of

100% and a specificity of 96.97% for thyroid disease diagnosis.

Table 5: Estimation of fetuin-A threshold, sensitivity, specificity and AUROC in thyroid patients

Parameters	Cut-off points	Sensitivity (%)	Specificity (%)	AUROC	*p*-value
Fetuin A (ng/ml)	8.5	100	96.97%	1	0.000

In Table 6, no significant correlation was observed between the specific parameter under study and thyroid hormones. Significantly, a correlation coefficient of r=0.8199 (p=0.000) demonstrated an emphatic positive association between Fetuin-A and FABP. In a parallel vein, T3 and T4 also demonstrated a positive relationship, reflected in a correlation coefficient of r=0.7904 (p=0.000). In stark contrast, TSH showcased an inverse relationship with both T3 and T4, substantiated by correlation coefficients of r= -0.5889 (p = 0.000) and r= -0.6203 (p = 0.000), respectively.

Table 6: Pearson correlation coefficients between thyroid disease research parameters and thyroid hormones

Parameter	Pearson correlation	T3	T4	TSH	FABP-4
T4	*r*	0.79			
	p-value	0.00			
TSH	*r*	-0.59	-0.620		
	p-value	0.0006	0.0003		
FABP-4	*r*	-0.256	-0.118	0.072	
	p-value	0.172	0.536	0.705	
Fetuin A	*r*	-0.245	-0.221	0.202	0.8199
	p-value	0.1921	0.2397	0.2849	0.0000

DISCUSSION

The thyroid gland plays a pivotal role in thermogenesis, sustaining basal metabolic rates, and managing lipid and carbohydrate metabolism, as well as influencing food consumption [1]. When thyroid function is compromised, the risk of metabolic conditions like hypertension, obesity, type 2 diabetes, and cardiovascular issues rises, potentially reducing life expectancy [4]. Variations in thyroid hormone levels have been observed in conditions such as thyroid disorders, dyslipidemia, glucose intolerance, and obesity. Thyroid dysfunction brings about a range of metabolic changes. A crucial aspect of metabolism is the signaling interplay between the thyroid and tissues central to energy balance. In conjunction with thyroid hormones, cytokines—like adipokines from adipose tissue and hepatocytes from the liver—aid in facilitating communication among various tissues. High levels of fetuin-A are connected to the beginning of insulin resistance because they affect an inhibitor of insulin receptor tyrosine kinase. Additionally, fetuin-A is frequently viewed as a key indicator for conditions like subclinical atherosclerosis, dyslipidemia, and obesity [15]. In this study, we observed a significant elevation in levels of fetuin-A in patients when compared to the control group. This finding aligns with results from studies by Pamuk *et al*. [16] and Ammar et al. [17]. Such outcomes underscore fetuin-A's potential as a marker for components of the metabolic syndrome, as indicated in a recent meta-analysis [18]. Bakiner *et al*. published findings that a marked reduction in plasma fetuin-A levels in hypothyroidism cases, with levels being 20% less than the control group (p=0.0001) [19]. Bakiner and others found that people with thyroid problems have higher levels of fetuin-A. They also discovered that as the level of TSH in the blood increases, the level of fetuin-A decreases. However, in this study, we did not find a relationship between fetuin-A and thyroid hormones. The increase in fetuin-A levels in hyperthyroidism may be linked to its effect on bone health. This is because a lack of fetuin-A can led to calcium buildup in soft tissues, and hyperthyroidism speeds up the process of bone turnover. It is believed that free fatty acids drive the elevated expression of fetuin-A, which draws macrophages to adipose tissue. Once there, they transition to the pro-inflammatory M1 subtype, further exacerbating inflammatory responses [20]. Thyroid hormones collaborate with fetuin-A to prevent the calcification of soft tissues. Physiological levels of T3, acting via thyroid hormone nuclear receptors, have been demonstrated to enhance Matrix gla protein (MGP) are vitamin-K dependent proteins that bind calcium in their γ-carboxylated versions in mammals)expression in Vascular smooth muscle cells (VSMC), offering protection against vascular calcification [21]. Meanwhile, fetuin-A and thyroid hormones appear to jointly regulate insulin sensitivity through shared pathways. Recent studies have also suggested that thyroid hormones directly influence fetuin-A expression. Alterations in thyroid status affect by regulating protein production in the liver and modulating RNA polymerase activity [22]. Interestingly, hyperthyroidism was characterized by an augmented protein synthesis, while its hypothyroid counterpart exhibited diminished synthesis. A study conducted in vitro on a liver cell line underscored the stimulatory impact of T3 on fetuin-A expression. Delving deeper into the molecular dynamics, T3's affinity to bind with thyroid receptor α1 emerges as pivotal, steering the regulation of a panoply of proteins, prominently featuring fetuin-A, by interacting with gene promoter territories [23]. In hypophysectomized rats, administration of T3 led to a rise in serum fetuin-A levels, reinforcing this notion. On the other hand, a study involving patients being tested for thyroid cancer recurrence found that using recombinant human TSH did not change the levels of serum fetuin-A. In numerous clinical explorations, as expounded in subsequent segments, the

concentration of fetuin-A appears to be intricately entwined with TSH. The hypothesis suggests that TSH might not have a direct impact on fetuin-A levels. It could mean that a constant low or high thyroid hormone level affects fetuin-A levels, possibly through ways related to T3. The health of the cardiovascular system is closely intertwined with thyroid functionality. Individuals with either manifest or latent hypothyroidism face an elevated risk of developing and exacerbating cardiovascular conditions [25]. Treatment of hyperthyroidism led to a notable reduction in fetuin-A concentrations. As the levels of thyroid hormones normalized, there was a corresponding decline in fetuin-A levels. A profound interrelation emerged between thyroid hormones and fetuin-A concentrations. Research shows that high levels of fetuin-A are often connected to hyperthyroidism, likely because it plays an important role in bone metabolism. Even though TSH concentrations might not have a direct effect on fetuin-A, they could signify an extended state of hyper- or hypothyroidism, with factors like T3 potentially modulating fetuin-A levels. Fetuin-A is involved in several important body functions, including inflammation, fat and protein metabolism, bone health, and the balance of calcium. FABP-4 has been identified as potentially beneficial in addressing thyroid complications [30], a finding that aligns with current results. Numerous studies have underscored a significant association between FABP4 and conditions like cardiovascular diseases and diabetes. Elevated levels of circulating FABP4 have been documented in humans with metabolic syndrome, obesity, insulin resistance, gestational diabetes, as well as type 1 and type 2 diabetes [28]. There's also evidence suggesting that lipotoxicity can adversely impact the thyroid gland, leading to hypothyroidism [31]. Increased levels of circulating FABP4 have also been linked to conditions such as hypertension, dyslipidemia, renal failure, and myocardial dysfunction [30]. It is plausible that thyroid hormones play a role in regulating FABP-4 expression in adipose tissue. However, while both animal and human studies have reported variations in FABP-4 levels in the context of thyroid dysfunction, a consensus on these findings remains elusive [31]. FABP4 has been distinguished as a linchpin in the genesis of atherosclerosis. This is because it can help create foam cells, encourage macrophages to absorb free fatty acids, and cause inflammation, which leads to weakened function of the blood vessel lining. Another study revealed that patients with hypothyroidism exhibited notably elevated levels of inflammatory myofibroblastic tumor (IMT) and TSH in comparison to their healthy counterparts. This research also indicated that FABP4 concentrations were more pronounced in individuals with hypothyroidism and exhibited a positive correlation with TSH levels [33]. Interestingly, the level of FABP4 was associated with measures used to assess how the body responds to thyroid hormones, like the thyroid-stimulating hormone index (TSHI) and the ratio of T3 to T4 hormones. Elevated FABP4 levels were indicative of diminished sensitivity as observed in these metrics [34]. Preclinical explorations have extolled the notion of zeroing in on FABP4 for the mitigation of metabolic maladies. Yet, the arcane conduits through which FABP4 might sway thyroid hormone responsiveness remain largely ensconced in mystery [35]. To specifically target FABP4, numerous small molecule inhibitors and antibodies have been developed [36]. A recent study by Prentice *et al.* suggested a potential connection between FABP4 and thyroid hormone sensitivity. The study examined euthyroid individuals and observed that elevated levels of FABP4 were associated with reduced thyroid hormone sensitivity. This was evident from indicators such as the quantile-based index for thyroid feedback, TSHI, and the T3/T4 ratio, which were employed to assess both central and peripheral responses to thyroid hormones [36]. Nie et al.'s research highlighted potential interconnections between health disorders like metabolic syndrome, non-alcoholic fatty liver disease, diabetes, hypertension, and heightened sensitivity to thyroid hormones. Intriguingly, patients diagnosed with hyperthyroidism exhibited raised FABP4 concentrations compared to those with regular thyroid functionality; however, these elevated levels normalized post-treatment [37]. Similarly, both overt and subclinical hypothyroid patients had greater FABP4 concentrations than their healthy counterparts. Associations were discerned between FABP4 levels and T3, T4, or TSH readings [38]. Additionally, it's suggested that FABPs may affect the internal processes related to the production of thyroid hormones and the functioning of T3 and T4 receptors, which could improve their signaling. This lends credence to the theory that FABPs might indirectly influence the onset and advancement of hyperthyroidism [39].

Conclusions

This study found a substantial link between circulating levels of FABP4, fetuin-A, and thyroid dysfunction groups, highlighting their possible relevance in metabolic abnormalities associated with thyroid problems. These findings are critical for the development of preventative and therapeutic strategies that address metabolic abnormalities in thyroid disorders.

ACKNOWLEDGEMENT

The authors thank the Specialized Centre for Endocrinology and Diabetes, Baghdad and to the volunteers who contributed their blood samples for the performing of this study.

Conflict of interests

No conflict of interest was declared by the authors.

Funding source

The authors did not receive any source of funds.

Data sharing statement

Supplementary data can be shared with the corresponding author upon reasonable request.

REFERENCES

1. Volke L, Krause K. Effect of thyroid hormones on adipose tissue flexibility. *Eur Thyroid J*. 2021;10(1):1–9. doi: 10.1159/000508483.
2. Taha KN, Risan FA, Mohammed AJ. Possible roles of micro RNA-142-5p and claudin-1 in development of Hashimoto's thyroiditis in Iraqi patients. *J Techniques*. 2022;4(2):50–55. doi: 10.51173/jt.v4i2.473.
3. Li HL, Wu X, Xu A, Hoo RL. A-FABP in metabolic diseases and the therapeutic implications: An update. *Int J Mol Sci*. 2021;22(17):9386. doi: 10.3390/ijms22179386.
4. Pal D, Dasgupta S, Kundu R, Maitra S, Das G, Mukhopadhyay S, et al. Fetuin-A acts as an endogenous ligand of TLR4 to promote lipid-induced insulin resistance. *Nat Med*. 2012;18(8):1279-1285. doi: 10.1038/nm.2851.
5. Zybek-Kocik A, Sawicka-Gutaj N, Domin R, Szczepanek-Parulska E, Krauze T, Guzik P, et al. Titin and dystrophin serum concentration changes in patients affected by thyroid disorders. *Endokrynol Pol*. 2021;72(1):1-7. doi: 10.5603/EP.a2020.0083.
6. García-Solís P, García OP, Hernández-Puga G, Sánchez-Tusie AA, Sáenz-Luna CE, Hernández-Montiel HL, et al. Thyroid hormones and obesity: a known but poorly understood relationship. *Endokrynol Pol*. 2018;69(3):292-303. doi: 10.5603/EP.2018.0032.
7. Sabri NW, Rashid BA, Shwiehk RS, Mahdy AH. Assessment of Risk Factors of Chronic Kidney Disease among Patients Attending Medical City Complex. *J Techniques*. 2023;5(2):147–154. doi: 10.51173/jt.v5i2.885.
8. Pala L, Monami M, Ciani S, Dicembrini I, Pasqua A, Pezzatini A, et al. Adipokines as possible new predictors of cardiovascular diseases: a case control study. *J Nutr Metab*. 2012;2012:253428. doi: 10.1155/2012/253428.
9. Alkharfy KM, Al-Daghri NM, Vanhoutte PM, Krishnaswamy S, Xu A. Serum retinol-binding protein 4 as a marker for cardiovascular disease in women. *PLoS One*. 2012;7(10):e48612. doi: 10.1371/journal.pone.0048612.
10. Fan J, Yin S, Lin D, Liu Y, Chen N, Bai X, et al. Association of serum retinol-binding protein 4 levels and the risk of incident type 2 diabetes in subjects with prediabetes. *Diabetes Care*. 2019;42(8):1574-1581. doi: 10.2337/dc19-0265.
11. Mohammed SN, Jassim WE, Mohammed NA. To investigate the associations of dyslipidemia and BMI, as risk factors leading to insulin resistance and development of type2 diabetes mellitus in Baquba city. *J Techniques*. 2022;4(3):27–33. doi: 10.51173/jt.v4i3.538.
12. Dadej D, Szczepanek-Parulska E, Ruchała M. Interplay between fatty acid binding protein 4, fetuin-A, retinol binding protein 4 and thyroid function in metabolic dysregulation. *Metabolites*. 2022;12(4):300. doi: 10.3390/metabo12040300.
13. Aleksandrova K, Drogan D, Weikert C, Schulze MB, Fritsche A, Boeing H, et al. Fatty acid-binding protein 4 and risk of type 2 diabetes, myocardial infarction, and stroke: A prospective cohort study. *J Clin Endocrinol Metab*. 2019;104(12):5991-6002. doi: 10.1210/jc.2019-00477.
14. Stefan N, Fritsche A, Weikert C, Boeing H, Joost HG, Häring HU, et al. Plasma fetuin-A levels and the risk of type 2 diabetes. *Diabetes*. 2008;57(10):2762-2767. doi: 10.2337/db08-0538.
15. Roshanzamir F, Miraghajani M, Rouhani MH, Mansourian M, Ghiasvand R, Safavi SM. The association between circulating fetuin-A levels and type 2 diabetes mellitus risk: systematic review and meta-analysis of observational studies. *J Endocrinol Invest*. 2018;41(1):33-47. doi: 10.1007/s40618-017-0697-8.
16. Pamuk BO, Yilmaz H, Topcuoglu T, Bilgir O, Çalan O, Pamuk G, et al. Fetuin-A levels in hyperthyroidism. *Clinics (Sao Paulo)*. 2013;68(3):379-383. doi: 10.6061/clinics/2013(03)oa15.
17. Ammar SR, Elbedewy TA, Nagy HM, Kotb, NA. Relationship between serum Fetuin-A and insulin resistance in patients with hyperthyroidism. *Tanta Med J*. 2027;45(3):135-140. doi: 10.4103/tmj.tmj_4_17.
18. Bakiner O, Bozkirli E, Ertugrul D, Sezgin N, Ertorer E. Plasma fetuin-A levels are reduced in patients with hypothyroidism. *Eur J Endocrinol*. 2014;170(3):411-418. doi: 10.1530/EJE-13-0831.
19. Icer MA, Yıldıran H. Effects of nutritional status on serum fetuin-A level. *Crit Rev Food Sci Nutr*. 2020;60(11):1938-1946. doi: 10.1080/10408398.2019.1631751.
20. Brix JM, Stingl H, Höllerl F, Schernthaner GH, Kopp HP, Schernthaner G. Elevated fetuin-A concentrations in morbid obesity decrease after dramatic weight loss. *J Clin Endocrinol Metab*. 2010;95(11):4877-4881. doi: 10.1210/jc.2010-0148.
21. Seo DY, Park SH, Marquez J, Kwak HB, Kim TN, Bae JH, et al. Hepatokines as a molecular transducer of exercise. *J Clin Med*. 2021;10(3):385. doi: 10.3390/jcm10030385.
22. Afrisham R, Paknejad M, Ilbeigi D, Sadegh-Nejadi S, Gorgani-Firuzjaee S, Vahidi M. Positive correlation between circulating fetuin-A and severity of coronary artery disease in men. *Endocr Metab Immune Disord Drug Targets*. 2021;21(2):338-344. doi: 10.2174/1871530320666200601164253.
23. Birukov A, Polemiti E, Jäger S, Stefan N, Schulze MB. Fetuin-A and risk of diabetes-related vascular complications: a prospective study. *Cardiovasc Diabetol*. 2022;21(1):6. doi: 10.1186/s12933-021-01439-8.
24. Nimptsch K, Janke J, Pischon T, Linseisen J. Association between dietary factors and plasma fetuin-A concentrations in the general population. *Br J Nutr*. 2015;114(8):1278-1285. doi: 10.1017/S0007114515002639.
25. Ix JH, Shlipak MG, Brandenburg VM, Ali S, Ketteler M, Whooley MA. Association between human fetuin-A and the metabolic syndrome: data from the Heart and Soul Study. *Circulation*. 2006;113(14):1760-1767. doi: 10.1161/CIRCULATIONAHA.105.588723.
26. Zachariah JP, Quiroz R, Nelson KP, Teng Z, Keaney JF, Sullivan LM, et al. Prospective relation of circulating adipokines to incident metabolic syndrome: The Framingham Heart Study. *J Am Heart Assoc*. 2017;6(7):e004974. doi: 10.1161/JAHA.116.004974.
27. Pan X, Kaminga AC, Chen J, Luo M, Luo J. Fetuin-A and fetuin-B in non-alcoholic fatty liver disease: A meta-analysis and meta-regression. *Int J Environ Res Public Health*. 2020;17(8):2735. doi: 10.3390/ijerph17082735.
28. Guo VY, Cao B, Cai C, Cheng KK, Cheung BMY. Fetuin-A levels and risk of type 2 diabetes mellitus: a systematic review and meta-analysis. *Acta Diabetol*. 2018;55(1):87-98. doi: 10.1007/s00592-017-1068-9.
29. Egbuche O, Biggs ML, Ix JH, Kizer JR, Lyles MF, Siscovick DS, et al. Fatty Acid binding protein-4 and risk of cardiovascular disease: The Cardiovascular Health Study. *J Am Heart Assoc*. 2020;9(7):e014070. doi: 10.1161/JAHA.119.014070.
30. Sujana C, Huth C, Zierer A, Meesters S, Sudduth-Klinger J, Koenig W, et al. Association of fetuin-A with incident type 2 diabetes: results from the MONICA/KORA Augsburg study and a systematic meta-analysis. *Eur J Endocrinol*. 2018;178(4):389-398. doi: 10.1530/EJE-17-1053.
31. Trojnar M, Patro-Małysza J, Kimber-Trojnar Ż, Leszczyńska-Gorzelak B, Mosiewicz J. Associations between fatty acid-binding protein 4: A proinflammatory adipokine and insulin resistance, gestational and type 2 diabetes mellitus. *Cells*. 2019;8(3):227. doi: 10.3390/cells8030227.
32. Lee CH, Lui DTW, Lam KSL. Adipocyte fatty acid-binding protein, cardiovascular diseases and mortality. *Front Immunol*. 2021;12:589206. doi: 10.3389/fimmu.2021.589206.
33. Garin-Shkolnik T, Rudich A, Hotamisligil GS, Rubinstein M. FABP4 attenuates PPARγ and adipogenesis and is inversely correlated with PPARγ in adipose tissues. *Diabetes*. 2014;63(3):900-9011. doi: 10.2337/db13-0436.
34. Furuhashi M. Fatty acid-binding protein 4 in cardiovascular and metabolic diseases. *J Atheroscler Thromb*. 2019;26(3):216-232. doi: 10.5551/jat.48710.
35. Sun J, Zhang D, Xu J, Chen C, Deng D, Pan F, et al. Circulating FABP4, nesfatin-1, and osteocalcin concentrations in women with gestational diabetes mellitus: a meta-analysis. *Lipids Health Dis*. 2020;19(1):199. doi: 10.1186/s12944-020-01365-w.
36. Prentice KJ, Saksi J, Robertson LT, Lee GY, Inouye KE,

Eguchi K, et al. A hormone complex of FABP4 and nucleoside kinases regulates islet function. *Nature*. 2021;600(7890):720-726. doi: 10.1038/s41586-021-04137-3.
37. Nie X, Ma X, Xu Y, Shen Y, Wang Y, Bao Y. Increased serum adipocyte fatty acid-binding protein levels are associated with decreased sensitivity to thyroid hormones in the euthyroid population. *Thyroid*. 2020;30(12):1718-1723. doi: 10.1089/thy.2020.0011.
38. Parra S, Cabré A, Marimon F, Ferré R, Ribalta J, Gonzàlez M, et al. Circulating FABP4 is a marker of metabolic and cardiovascular risk in SLE patients. *Lupus*. 2014;23(3):245-254. doi: 10.1177/0961203313517405.
39. Shu L, Hoo RL, Wu X, Pan Y, Lee IP, Cheong LY, et al. A-FABP mediates adaptive thermogenesis by promoting intracellular activation of thyroid hormones in brown adipocytes. *Nat Commun*. 2017;8:14147. doi: 10.1038/ncomms14147.