



Adipocyte Fatty Acid Binding Protein Level among Patients with Subclinical Hypothyroidism

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ABSTRACT:

BACKGROUND:

Subclinical hypothyroidism is typically diagnosed when free thyroxine level (fT4) is normal and thyroid stimulating hormone level is elevated. The prevalence of subclinical hypothyroidism is 3-15%. Adipocyte fatty acid binding protein (A-FABP) is an adipokine secreted from adipose tissue. It has a role in the regulation of lipid storage, oxidation and lipolysis. Atherogenic indices of plasma are lipid ratios that are used in predicting cardiovascular events. They include atherogenic index of plasma, Castelli's risk indexes I and II and atherogenic coefficient.

OBJECTIVE:

The study aimed to evaluate serum A-FABP level among subclinical hypothyroidism patients compared to a control group.

MATERIALS AND METHOD:

A cross-sectional study was conducted at Azadi teaching Hospital/ Duhok city starting from Nov, 2022 until Dec, 2023. It included 160 participants, 80 were newly diagnosed subclinical hypothyroidism cases and 80 were apparently healthy control. Venous blood samples were obtained from each participant after an overnight fast for the following biochemical tests: thyroid stimulating hormone, free triiodothyronine, free thyroxine, anti-thyroid peroxidase antibody, lipid profile and serum A-FABP. All analytes were measured using automated clinical chemistry analyzer Cobas 6000 (Roche-HITACHI) except for A-FABP that was measured using enzyme linked immune sorbent assay.

RESULTS:

The majority of the participants were aged less than 40 years (78.8%) with females' predominance (75%). The mean BMI (28.4 kg/m²) and mean waist circumference (91.7 cm) of patients were significantly higher than control participants ($p = 0.035$) and ($p = 0.033$) respectively. No significant differences were detected between cases and controls in the mean of total cholesterol, triglycerides, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol. No significant differences were detected of atherogenic indices between the cases and controls. The mean A-FABP level among cases (3.11 ng/ml) was significantly ($p = 0.030$) higher than that of the control group which was 2.63 ng/ml.

CONCLUSION:

The mean level of serum A-FABP was significantly higher among patients with SCH compared to healthy control group.

KEY WORDS: Adipocyte fatty acid binding protein; free thyroxine; lipid profile; subclinical hypothyroidism.

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INTRODUCTION:

Subclinical hypothyroidism (SCH) is typically defined as normal free thyroxine (fT4) level and elevated thyroid stimulating hormone (TSH) level. SCH patients are asymptomatic most of the time and they are diagnosed accidentally by laboratory testing ⁽¹⁾. The prevalence of subclinical hypothyroidism is estimated to be between 3-15% according to population studies ⁽¹⁾. It is more

common in elderly women with a prevalence ranging between 5-20% ⁽²⁾. Globally, the most common etiology of SCH is chronic autoimmune thyroiditis ^(1,2). The turning risk of SCH to overt hypothyroidism (OH) is 2-6% per year, and mostly higher in those with serum TSH levels more than 10 mIU/m and abnormally high thyroid peroxidase antibodies (TPOAb) ⁽¹⁾.

Adipocyte fatty acid binding protein (A-FABP) or fatty acid binding protein 4 (FABP4) or adipocyte protein 2 (aP2) is one of the bioactive-peptide adipokine⁽³⁾. A-FABP is produced and secreted predominantly from adipocytes that is under the control of the gene AFABP or FABP4⁽³⁾. A-FABP acts as a lipid chaperone that regulate and facilitate trafficking of non-esterified fatty acids throughout intracellular compartments, as well as, it regulates lipid storage, oxidation and lipolysis through interaction with hormone sensitive lipase (HSL) and a co-activator of the adipose triglyceride lipase (ATGL)^(4,5). In obese population, there is increased circulating A-FABP due to expansion in adipose tissue and increased rate of lipolysis leading to increase efflux of free fatty acids that enhances A-FABP release⁽⁴⁾. Serum A-FABP plays a crucial role in the development of insulin resistance and atherosclerosis due to chronic inflammatory process as it inhibits endothelial nitric oxide synthetase in the smooth muscles^(6,7). This adipokine also promotes atherosclerosis via altering lipid metabolism in the macrophages and facilitated foam cell formation that causes atherogenic effects⁽⁴⁾.

Dyslipidemia is considered as a recognized risk-factor for cardiovascular diseases (CVD) and defined as an elevation in the low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC) and triglyceride (TG) and decreases in high-density lipoprotein cholesterol (HDL-C)⁽⁸⁾. Atherogenic indices are lipid ratios that are used in predicting cardiovascular events and efficacy of therapy specially in the presence of normal serum lipid profile⁽⁹⁾. Atherogenic indices include the following: atherogenic Index of plasma (AIP), Castelli's risk indexes I and II (CRI-I and CRI-II) and atherogenic coefficient (AC)⁽⁹⁾.

SCH has been linked to cardiovascular risk factors such as dyslipidemia, atherosclerosis and hypertension⁽¹⁰⁾. The association of SCH with dyslipidemia is mostly due to reduction in number of low-density lipoprotein receptors, decreased cholesterol breakdown and decreasing the fractional clearance of LDL-C^(10,11). However, dyslipidemia in patients with SCH is still a topic of debate as there is controversy in pervious literature^(12,13,14).

This study was aimed to evaluate serum A-FABP level among patients with SCH disorder and apparently healthy control group, and to find out if this has association with atherogenic indices of plasma.

MATERIALS AND METHODS:

A cross-sectional study was conducted at Azadi Teaching Hospital - Duhok city - Kurdistan region - Iraq. The study started from Nov 2022 until Dec 2023, and enrolled 160 participants, 80 with newly diagnosed SCH, and 80 were apparently healthy control.

Ethical consent was obtained from the research committee of the Directorate of health of Duhok Governorate. Reference number: 26102022-8-2.

Inclusion and exclusion criteria of the study:

inclusion criteria: newly diagnosed patients who fulfill the criteria of SCH including higher TSH than reference range > 4.2 microIU/mL, and fT4 and fT3 within the reference range (3.1 – 6.8 pmol/L) and (12 – 22 pmol/L) respectively⁽¹⁵⁾. Those patients must not be complaining of previously diagnosed thyroid disorders.

Exclusion criteria: Factors and diseases that have effect on thyroid function tests including: pregnancy, patients with any chronic diseases such as hypertension, DM, kidney diseases, liver diseases and chronic inflammatory diseases, patients with cancer previously or newly diagnosed, patients who underwent recent surgery and patients who had been receiving treatment that interfere with thyroid function tests such as steroid, iodine, amiodarone and oral contraceptive pills.

Data collection:

Cases participants were collected from out-patients who were attending endocrine and diabetic unit of Azadi Teaching Hospital. The identified cases of SCH were notified, and it was made sure they fit into the study's inclusion and exclusion criteria by taking a brief history.

Control participants were collected, from relatives and acquaintances, after the cases accordingly, as they had matching age and gender with the cases. They were apparently healthy subjects that, to their knowledge, free of chronic diseases.

After taking a verbal consent from all participants on being part of the study, they were asked to fast overnight for 10-12 hours and to attend biochemistry unit of laboratory department of Azadi Teaching Hospital in the next early morning.

Assessment of participants:

Upon receiving the participants in the laboratory, a questionnaire was given to them that included questions about: full name, age, sex, address, medical and surgical history, drugs history, and their written consent on being part in the study. The anthropometric measures of the participants were measured and included: weight in kilograms,

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height in centimeter and waist circumference in centimeters. The high cut-off points of waist circumference were as follows: for males ≥ 102 and for females ≥ 88 ⁽¹⁶⁾. Body mass index (BMI) of each participant was calculated according to the formula kg/m^2 (weight in kilogram divided on square of height in meters). BMI from 18.5% - 24.9% was the normal desired weight, from 25% - 29.9% is overweight, whereas BMI of above 30.0 % was considered obese ⁽¹⁷⁾.

10 ml of venous blood was collected from each participant. The samples were centrifuged for 20

minutes at 3000 revolutions per minute to obtain the serum. Serum was processed for a number of biochemical tests included: TSH, fT4, fT3, anti-TPO, lipid profile (TC, HDL-C, LDL-C, TG) and A-FABP. A-FABP was estimated using ELISA technique, whereas, all other parameters were measured by Cobas 6000 (Roche-HITACHI) based on Electrochemiluminescence (ECL) and enzymatic colorimetric method.

Atherogenic indices were calculated according to their corresponding equations as follows ^(9,18):

$$\text{AIP} = \log \left(\frac{\text{TG}}{\text{HDL-C}} \right), \text{CRI-I} = \frac{\text{TC}}{\text{HDL-C}}, \text{CRI-II} = \frac{\text{LDL}}{\text{HDL-C}}, \text{AC} = \frac{\text{nonHDL-C}}{\text{HDL-C}}$$

Reference range for the lipid profile were according to national cholesterol education program ATP III NCEP as follows: TC mg/dl: < 200 desirable, 200-239 moderate risk, > 240 high risk, HDL-c mg/dl: ≥ 60 no risk, LDL-c mg/dl: <100 optimal, 100-129 near optimal, 130-159 boarder-line high, 160-189 high, >190 very high, TG: up to 150 mg/dl ⁽¹⁹⁾. Cut-off values of atherogenic indices were as follows: AIP, levels of < 0.11 as low risk, between 0.11 and 0.21 as intermediate risk, and >0.21 as high risk, For CRI-I, the cut-off point was <5 and ≥ 5 as low and high risk respectively, CRI-II, cut-off points were <3 for low risk and ≥ 3 for high risk, AC levels of < 2.1 as low risk and ≥ 2.1 as high risk ^(20,21,22).

Statistical analysis

Data were analyzed using the Statistical Package for Social Sciences (SPSS, version 26). Chi square test of association was used to compare proportions

of two groups. Fisher's exact test was used when the expected frequency (value) was less than 5 of more than 20% of the cells of the table. Student's t test (unpaired t test) was used to compare two means. A p value of ≤ 0.05 was considered as statistically significant.

RESULTS:

Table 1 shows that the mean age was 32.9 years, majority (78.8%) of participants were aged less than 40 years and (75%) were females. The table shows that (37.5%) of the cases were obese compared with (25%) of the controls ($p = 0.247$). The mean BMI of cases (28.4 Kg/m²) was significantly ($p = 0.035$) higher than that of the controls (26.7 Kg/m²). furthermore; (52.5%) of cases had high waist circumference, the mean waist circumference of cases (91.7 cm) was significantly ($p = 0.033$) higher than that of the controls (87.4 cm).

Table 1: Basic characteristics and anthropometric data of the studied subjects.

	Cases No. (%)	Controls No. (%)	Total No. (%)	P-value
Age (years)				
< 40	63 (78.8)	63 (78.8)	126 (78.8)	
≥ 40	17 (21.3)	17 (21.3)	34 (21.3)	> 0.999 *
Mean (SD) years	32.9 (8.9)	32.9 (8.9)		> 0.999†
Gender				
Male	20 (25.0)	20 (25.0)	40 (25.0)	
Female	60 (75.0)	60 (75.0)	120 (75.0)	> 0.999*
BMI				
Underweight	2 (2.5)	1 (1.3)	3 (1.9)	
Normal	20 (25.0)	29 (36.3)	49 (30.6)	
Over-weight	28 (35.0)	30 (37.5)	58 (36.3)	
Obese	30 (37.5)	20 (25.0)	50 (31.3)	0.247**
Mean (SD) Kg/m²	28.4 (5.23)	26.7 (4.9)		0.035†
Waist circumference				
Normal	38 (47.5)	48 (60.0)	86 (53.8)	
High	42 (52.5)	32 (40.0)	74 (46.2)	0.113*
Mean (SD)	91.7 (13.6)	87.4 (12.0)		0.033†
Total	80 (100.0)	80 (100.0)	160 (100.0)	

* By Chi square test. **By Fisher's exact test. †By Unpaired t test.

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Table 2 shows biochemical results of the participants. The mean TSH level of patients with SCH was significantly higher than those of controls ($p < 0.001$), with 38.7% were positive for anti-TPO and a significantly higher mean anti-TPO level ($p < 0.001$). No significant differences were detected between patients and controls in the mean of TC ($p = 0.145$), TG ($p = 0.084$), HDL-c ($p = 0.281$), and LDL-c ($p = 0.839$). Regarding A-FABP, its mean(SD) 3.11 (1.67) ng/ml was significantly ($p = 0.030$) higher than healthy controls 2.63 (1.02) ng/ml.

Table 2: Biochemical parameters among study participants.

	Cases		Controls		P-value
	Mean	(SD)	Mean	(SD)	
TSH (microIU/mL)	6.46	(1.57)	2.55	(1.08)	< 0.001†
fT3 (pmol/ml)	3.44	(0.47)	3.48	(0.34)	0.558†
fT4 (pmol/ml)	14.78	(2.03)	17.26	(1.99)	< 0.001†
Anti-TPO (IU/mL)	51.18	(2.89)	16.43	(14.56)	< 0.001†
Anti-TPO categories No. (%)					
< 30	49	(61.3)	72	(90.0)	
≥ 30	31	(38.7)	8	(10.0)	< 0.001*
Cholesterol (mg/dl)	159.71	(30.19)	153.15	(26.33)	0.145†
Triglycerides (mg/dl)	107.68	(79.44)	90.26	(41.18)	0.084†
HDL (mg/dl)	44.61	(10.00)	42.80	(11.18)	0.281†
LDL (mg/dl)	93.23	(26.09)	92.40	(25.03)	0.839†
A-FABP (ng/ml)	3.11	(1.67)	2.63	(1.02)	0.030†

*By Chi square test. The other p values were calculated by † the unpaired t test.

Table 3 shows an insignificant difference of atherogenic indices between SCH patients and control as follows: AIP ($p = 0.864$), CRI-I ($p = 0.260$), CRI-II ($p = 0.224$), and AC ($p = 0.736$). Around two thirds of the cases and controls were from the high-risk subgroup of atherogenic index of plasma (AIP), and more than two thirds of the cases and controls fall within the high-risk subgroup of atherogenic coefficient (AC).

Table 3: Atherogenic indices among study participants.

	Cases	Controls	Total	P-value
	No. (%)	No. (%)	No. (%)	
AIP				
Low risk	24 (30.0)	24 (30.0)	48 (30.0)	
Intermediate risk	9 (11.3)	7 (8.8)	16 (10.0)	
High risk	47 (58.8)	49 (61.3)	96 (60.0)	0.864*
Mean (SD)	0.32 (0.30)	0.29 (0.27)		0.590†
CRI-I				
< 5	71 (88.8)	66 (82.5)	137 (85.6)	
≥ 5	9 (11.3)	14 (17.5)	23 (14.4)	0.260*
Mean (SD)	3.77 (1.19)	3.83 (1.24)		0.753†
CRI-II				
< 3	68 (85.0)	62 (77.5)	130 (81.2)	
≥ 3	12 (15.0)	18 (22.5)	30 (18.8)	0.224*
Mean (SD)	2.21 (0.84)	2.36 (1.02)		0.306†
AC				
< 2.1	27 (33.8)	25 (31.3)	52 (32.5)	
≥ 2.1	53 (66.3)	55 (68.7)	108 (67.5)	0.736*
Mean (SD)	2.77 (1.19)	2.83 (1.24)		0.753†
Total	80 (100.0)	80 (100.0)	160 (100.0)	

*Chi square test. †Unpaired t test.

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Comparing mean and frequency of atherogenic indices and A-FABP between SCH patients with TSH levels less than 10 μ IU/ml and those with TSH level of more than 10 μ IU/ml were shown in

table 4. There were insignificant differences between all atherogenic indices and A-FABP: AIP ($p = 0.213$), CRI-I ($p = 0.386$), CRI-II ($p = 1.000$), AC ($p = 1.000$) and A-FABP ($p = 0.427$).

Table 4: Atherogenic indices by TSH level (cut off point of 10 microIU/ml) among patients with subclinical hypothyroidism.

	TSH (microIU/ml)		Total	P-value
	< 10 (76) No. (%)	\geq 10 (4) No. (%)		
AIP				
Low risk	22 (28.9)	2 (50.0)	24 (30.0)	
Intermediate risk	8 (10.5)	1 (25.0)	9 (11.3)	
High risk	46 (60.5)	1 (25.0)	47 (58.8)	0.213*
Mean (SD)	0.31 (0.29)	0.43 (0.61)		0.724**
CRI-I				
< 5	68 (89.5)	3 (75.0)	71 (88.8)	
\geq 5	8 (10.5)	1 (25.0)	9 (11.3)	0.386*
Mean (SD)	3.74 (1.12)	4.40 (2.34)		0.614**
CRI-II				
< 3	64 (84.2)	4 (100.0)	68 (85.0)	
\geq 3	12 (15.8)	0 (0.0)	12 (15.0)	> 0.999*
Mean (SD)	2.21 (0.85)	2.12 (0.64)		0.840**
AC				
< 2.1	26 (34.2)	1 (25.0)	27 (33.8)	
\geq 2.1	50 (65.8)	3 (75.0)	53 (66.3)	> 0.999*
Mean (SD)	2.74 (1.12)	3.40 (2.34)		0.614**
A-FABP				
Mean (SD)	3.14 (1.71)	2.45 (0.10)		0.427**
Total	76 (100.0)	4 (100.0)	80 (100.0)	

*By Fisher's exact test. **By unpaired t test.

DISCUSSION:

The present study shows that 75% of the SCH participants were females. It is known that thyroid diseases including SCH are more common in females than males^(11,23,24). Our study in concordance with previous studies have shown this. The etiology of this increased female's prevalence is not clear, but it is in part due to increased autoantibody in females and its relation to estrogen levels in the reproductive age^(25,26). Around 5-15% of female's population are positive to one of thyroid auto-antibodies, whether it is anti-thyroid peroxidase antibody (anti-TPO) or anti-thyroglobulin antibody⁽²⁶⁾. A woman body with high levels of estrogen and hormonal variation in different stages of menstrual cycle makes thyroid disorders more common in females⁽²⁵⁾.

The majority of the patients with SCH were aged less than 40 years old. These results are in

agreement with another study that shown the highest prevalence of SCH was between 30 and 40 years⁽²⁷⁾.

Obesity has effect on hypothalamic-pituitary-thyroid axis and deiodinase, so it is closely related to thyroid diseases⁽²⁸⁾. The results of this study show that more participants of SCH were obese (37.5%) compared to the control group (25%). Although this difference was statistically not significant ($p = 0.247$), the mean BMI of cases was significantly higher than those of control ($p = 0.035$). These results were in line with a study that had confirmed the prevalence of SCH was more common in obese people⁽²⁸⁾. The positive association between obesity and high TSH level is in part due to reduced expression of TSH gene in adipose tissue, so as a compensatory mechanism, TSH level becomes higher. Also, high levels of

leptin in obese people have an effect on increased secretion of thyrotropin releasing hormone as it increases its gene expression in the hypothalamus⁽²⁸⁾.

The results of this study have also shown that the mean waist circumference was significantly higher in cases compared to that of control group. The increased waist circumference along with the increased BMI indicates that obesity in the study group was mostly central obesity rather than lean mass. Meng-Ting Tsou in their study had concluded that even mild hypofunction of thyroid gland is contributable to abnormal fat distribution in the body⁽²⁹⁾.

Dyslipidemia is considered as the most important modifiable risk factor in the development of CVD⁽⁸⁾. Regarding the association of SCH with dyslipidemia, some of the previous studies showed positive correlation^(12,30,31), while others didn't show any significant difference^(11,14). The present study results show that TC, TG and LDL-c of the SCH patients were insignificantly higher than the control participants. These results were in concordance with Bhattarai et al and Kazheen H. et al studies that observed insignificantly higher levels in lipid profile in patients with SCH compared to control^(11,32). On the other hand, Qasim B, et al have shown that patients with SCH have dyslipidemia compared to control group and is considered an atherogenic status⁽³⁰⁾.

The explanation for this controversial literature could be due to several reasons. One of them is the age range of the participants is different among previous studies, and it is well known that TG and TC is affected by age⁽³²⁾. Also, there is increased prevalence of dyslipidemia globally in the general population, especially with nowadays lifestyle⁽³³⁾. This makes the defect in the control participants; they seem healthy but they could be suffering from hidden dyslipidemia.

This study aimed to further analyze lipid parameters by calculating atherogenic indices and linking it to SCH patients. Atherogenic indices have been used recently as a substitute for more complicated predictors of cardiovascular risk such as sdLDL marker⁽³⁴⁾. The study results did not find any significant difference between the cases and controls for all atherogenic indices including AIP, CRI (I and II) and AC. In contrary to these results, a study in India reported higher levels of AIP in SCH women, suggesting early detection and monitoring of dyslipidemia in SCH patients and early initiation of treatment⁽³⁵⁾. Although our study

results did not show any significant difference, it is worth mentioning that the majority of the participants from both the cases and controls fell within the high-risk group for two of the measured indices, AIP and AC. This further support our previous conclusion that

hyperlipidemia nowadays is common in the general population and it's not just related to specific disorders.

Both A-FABP and SCH have positive association with BMI, obesity, insulin resistance and dyslipidemia^(4,10,36,37), but to the date, there is controversial between different thyroid status and its relationship to serum A-FABP levels^(7,38,39). In the present study, the most important finding was a significantly higher mean A-FABP among patients with SCH compared to healthy control. This result was in concordance with TAN et al study that showed a high A-FABP in patients with overt hypothyroidism and SCH⁽⁷⁾. We assume that the link between SCH and elevated levels of A-FABP could be contributable to body fat content, as patients with SCH have more obesity than healthy people⁽³¹⁾, and previous reports have shown improvement of A-FABP levels after weight loss and bariatric surgery⁽⁶⁾.

On the other hand, two previous studies have associated A-FABP positively with hyperthyroidism^(38,39). The explanation for this is that A-FABP could be positively associated with autoimmunity as most of the cases of hypothyroidism, hyperthyroidism and SCH are caused by autoimmunity. The results of this study have also demonstrated significantly higher anti-TPO level in cases compared to controls ($p < 0.001$). This hypothesis is further supported by a previous study that was done on a group of patients with Hashimoto thyroiditis (HT) who have achieved euthyroid status and a group of control healthy subjects. It was found that A-FABP was higher in HT patients⁽⁵⁾. Also, increased serum A-FABP in female gender, supports both of our hypothesis relating A-FABP to body fat content and autoimmunity as females have more autoantibodies and more fat content in their bodies than males⁽²⁶⁾.

It was noticed in this study results that TSH level cut-off point at 10 microIU/ml didn't make a difference in the outcome of atherogenic indices and the level of serum A-FABP. This is explained by a meta-analysis study that has showed that thyroid hormones levels particularly T4 has

stronger association with biochemical parameters than do TSH level⁽⁴⁰⁾.

CONCLUSION:

The current study concluded that the level of serum A-FABP is higher among patients with SCH compared to healthy control group. But SCH disorder had no effect on lipid parameters as well as atherogenic indices of plasma.

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Conflict of interest: The authors declare that there is no conflict of interest.

Ethical approval:

1- Ethical consent obtained from the research committee of the Directorate of health of Duhok Governorate on 26 oct. 2022. Reference number: 26102022-8-2

2- Verbal and signed written consent were obtain from each participant individually, prior to their engagement in this study.

Authors contribution:

[Rezan Mohammed Hussein]: conceptualization, data curation, investigation, methodology, resources, visualization, writing – original draft, writing, and editing.

[Sherwan Ferman Salih]: methodology, project administration, supervision, writing – reviewing and editing.

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