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Thyroid dysfunction is not influencing serum asprosin levels in patients with retinopathy.

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ABSTRACT

Background: Thyroid hormones, namely triiodothyronine (T3) and thyroxin (T4) and the major regulatory hormones of metabolic processes that impact the metabolism of carbohydrates, lipids, and proteins. Asprosin is a novel glucogenic hormone that triggers the liver to release glucose into the bloodstream; thereby, this hormone is probably affected by any thyroid dysfunction.

Objective: The current study aims to delineate whether abnormal levels of thyroid hormones, namely T3 and T4, have a significant association with asprosin levels in patients with retinopathy.

Methods: In the present case-control study, we employed 83 participants distributed as 56 patients with retinopathy and 27 healthy controls. We measured T3, T4, asprosin, glycated hemoglobin (HBA1c), and fasting blood sugar (FBS).

Results: There is no significant association between asprosin and low levels of T3 and T4 in patients with retinopathy. Decreased T3 and T4 levels were significantly ($p > 0.05$) associated with an increased probability of developing retinopathy. No significant changes in the serum asprosin level in patients with retinopathy.

Conclusion: Asprosin hormone is probably not involved in the pathophysiology of retinopathy, and the impaired T3 and T4 in patients with retinopathy were not associated with asprosin levels.

Keywords: *Retinopathy, Asprosin, TSH, T3 and T4*

1. INTRODUCTION

One of the most prevalent microvascular consequences of type 2 diabetes mellitus (T2DM) is diabetic retinopathy (DR), which increases the societal and financial burden (Zhang, Saaddine et al. 2010). The World Health Organization (WHO) estimates that in 2006, there were 37 million cases of blindness worldwide, and DR-related blindness accounted for 4.8% of those cases(Zheng, He et al. 2012). The etiology of DR involves hyperglycemia and Retinal Microvasculopathy, Inflammation and, degeneration of the retina (Wang and Lo 2018, Abdul Jaleel, Almulla et al. 2022). Furthermore, it has become obvious that there are additional, as yet undisclosed risk factors for the disease, even while hyperglycemia, duration of diabetes, high blood pressure, and microalbuminuria are recognized to confer increased risk for the development and progression of DR (Busik 2021). Moreover, researchers have hypothesized that elevated plasma lipids and lipoproteins are risk factors for DR, particularly in the form of hard exudates (Busik 2021).

The most frequent endocrinopathies seen in clinical practice are thyroid disease and diabetes mellitus (DM, a major cause of DR), which often have complex interplaying mechanisms (Stefanowicz-Rutkowska, Baranowska-Jurkun et al. 2020). The thyroid gland's hormones control glucose and insulin production, but DM also interferes with the thyroid's ability to perform its function (Stefanowicz-Rutkowska, Baranowska-Jurkun et al. 2020). The development of the retina and the rise in retinal vascular density are both influenced by the hypothalamic-pituitary-thyroid axis(Martino, Seo et al. 1980, Mendoza and Hollenberg 2017). The animal-based model showed that Sirtuin 2 (SIRT-2) protein levels in the retinal ganglion cell layer were lower after induced hypothyroidism, which suggests that thyroid hormones substantially impact the normal development of retinal cytoarchitecture (Kocaturk, Ergin et al. 2016). Consequently, impairment of the thyroid gland significantly affects and induces abnormal lipid profiles (Rizos, Elisaf et al. 2011). Patients with DR experienced dyslipidemia more frequently than those in the control group (Popescu and Moţa 2009). Moreover, it has been reported that

the occurrence of DR is probably induced by abnormal lipid hemostasis (Stefanowicz-Rutkowska, Baranowska-Jurkun et al. 2020). Abnormal

lipid metabolism probably induces impaired adipose tissue-release hormones (Jung and Choi 2014). It has long been known that adipocytes function as both a storage facility for fat and have a role in expressing endocrine organs within the endocrine system (Trayhurn and Beattie 2001). It controls many physiological and pathological processes when seen as a key source of adipokines (Fasshauer and Blüher 2015). Several adipokines, such as irisin, leptin, adiponectin or adipsin, resistin, and visfatin, exhibit a multifunctional, multidirectional impact (Ouchi, Parker et al. 2011). Another multifunctional adipokine known as aprosin has recently been the subject of research studies and is thought to be a viable anti-obesity treatment (Ouchi, Parker et al. 2011).

The production of metabolically active molecules, such as adipokines, by adipose tissue is important for maintaining energy homeostasis and participating in several metabolic pathways, the inflammatory cascade, and pathophysiological processes that lead to obesity-related cardio-metabolic complications (Ouchi, Parker et al. 2011, Mancuso 2016). In this term, a novel adipokine was identified in 2016 named asprosin, which plays a role in glucose homeostasis and the control of food intake and energy homeostasis (Mazur-Bialy 2021). The C-terminal cleavage product is a 140 amino acid-long protein that is encoded by exons 65 and 66 of the fibrillin 1 gene (FBN1) on chromosome 15q21.1 (Ovali and Bozgeyik 2022). Although adipocytes appear to be the only cells capable of producing asprosin, white adipose tissue is the primary source of this adipokine's secretion (Romere, Duerrschmid et al. 2016). Since thyroid dysfunction may influence lipid metabolism (Duntas and Brenta 2018), we speculate that unbalanced thyroid hormones probably trigger abnormal asprosin levels, and they may be associated with the pathophysiology of retinopathy.

Nonetheless, no studies were reported concerning the association between asprosin and thyroid biomarkers, namely TSH, T3, and T4, along with their possible role in the diagnosis of retinopathy. Thus, in the present study, we aim to examine serum TSH, T3, T4, and asprosin levels in patients with retinopathy and delineate whether these markers can predict the diagnosis of the illness. This aim is based on our specific hypothesis, which states thyroid functions are significantly impaired in DR, which may alter asprosin levels by affecting adipocytes.

2. MATERIAL AND METHODS

Participants

We recruited 83 individuals in the current study, which were distributed into two groups: patients with retinopathy (n=56) and age-gender-matched healthy control (n=27). Eleven out of 83 patients were diagnosed with non-diabetic retinopathy, whereas all the rest were diabetic retinopathy. Moreover, retinopathy was non-proliferative in 50% of the patients and proliferative in the second 50%. Both groups of the study were collected from January to August 2021 from Amir Al-Muminin hospital in Najaf, Iraq. Healthy control group, including either workers of the hospitals or friends of the author. RT patients involved 45 patients who developed RT due to type 2 diabetes mellitus and 11 patients with non-diabetic retinopathy. We excluded any participant with a) thyroid diseases and those under thyroid hormone therapy, b) chronic inflammatory diseases, c) Type 1 diabetes mellitus or other diabetes mellitus, d) nephropathy, neuropathy, or any other complication. A senior specialized ophthalmologist was employed in the current study to diagnose patients with RT utilizing ophthalmoscopy and fundus imaging techniques. The same ophthalmologist classified RT as either non-diabetic and non-proliferative (NPDR) or proliferative diabetic retinopathy. Before enrollment in the present study, written informed consent was provided by all participants. The present study was approved by the International review board (IRB) at the university of Kufa with document number (no. 349/2021), which followed the Declaration of Helsinki's International Guideline for Human Research Protection.

Clinical and biochemical measurement

We employed an organized questionnaire to gather all socio-demographic information, including age, sex, duration of illness, smoking, and hypertension. We computed body mass index (BMI) by the equation dividing body weight in kilograms by height in meters. Venous fasting blood samples were collected in serum gel tubes between (9-11 A.M.) from the patients following overnight fasting. After assessing HBA1c, we left the sample in 10 minutes incubation at room temperature also, to ensure that the blood had been clotted, we centrifuged the sample to get serum, which aliquot in multiple small Eppendorf and stored in – 80 Celsius until the time of measurement. We recruited I-chroma device to assess glycosylated hemoglobin (HBA1c). Fasting blood sugar was measured by a commercial colorimetric kit provided by Cromatest, Spain. Furthermore, ELISA kits from Monobind Inc. Lake Forest company, USA were used to determine T3, T4 and TSH levels in serum. In contrast, serum asprosin level was measured ELISA, kit provided by Biobase company, China.

Statistical analysis

We used SPSS software version 27 on windows to analyze our data of the current study. Normality was tested via Kolmogorov–Smirnov test. We employed t-test to compare continuous variables between patients and healthy control, whereas Chi-square test utilized for categorical variables. A person correlation test was used to examine the correlation

between measured variables. Moreover, we used binary logistic regression to check the ability of the assessed biomarker to predict the diagnosis of the illness. We considered a statistical significance when the p-value.

Table 1: Socio-demographic and clinical characteristics of retinopathy patients (RT) and Healthy control (HC).

Variables	HC(n=27)	RT(n=56)	t	df	P-Value
Age	49.19(7.9)	55.16(11.12)	-2.499	81	0.014
Sex (M/F)	17/10	29/27	0.921	-	0.337
Smoking (Y/N)	7/20	7/49	2.342	-	0.126
Hypertension(Y/N)	0/27	37/19	32.18	-	0.000
BMI	24.44(4.67)	29.49(4.68)	-4.606	81	0.000
Asprosin	21.66(6.46)	21.97(14.57)	-0.106	81	0.916
TSH	-0.247(0.505)	0.119(1.14)	-1.588	81	0.116
T3	3.27(0.491)	2.25(0.705)	4.935	81	0.000
T4	16.10(1.32)	14.41(2.33)	3.486	81	0.000
FBS	100.81(13.2)	205.91(60.84)	-8.849	81	0.000
HbA1C	5.14(0.458)	8.80(2.11)	-8.845	81	0.000

Results

Comparison between retinopathy patients and healthy control

A comparison study in Table 1 indicates that patients with retinopathy showed significantly (<0.001) decreased T3 and T4 levels while there was no significant difference in TSH and asprosin levels. Table 1 also showed a significant difference (<0.001) between patients and healthy control in HBA1c, BMI, age, and hypertension. Moreover, no significant differences were found in gender and smoking.

M:Male, F: Female, Y: Yes, N: No, BMI: Body Mass Index, TSH: Thyroid stimulating hormone, T3: Triiodothyronine, T4: Thyroxine, FBS: Fasting blood sugar, HbA1c: Glycated hemoglobin

Table 2: Correlation results of Asprosin,TSH, T3 and T4 with all other variables.

Variables	Asprosin	TSH	T3	T4
Age	0.226*	0.143	-0.203*	-0.119
BMI	-0.165	-0.108	-0.286**	-0.025
Sex	-0.114	-0.005	-0.017	-0.035
Smoking	-0.016	-0.138	0.114	-0.299**
Hypertension	0.070	0.163	-0.279*	-0.282**
Asprosin	-	-0.058	0.088	0.058
TSH	-	-	0.141	-0.104
T3	-	-	-	0.239*

Correlation study of demographic characteristics with thyroid markers and asprosin

Table 2 shows the correlation between asprosin, TSH, T3, and T4 and other variables. There is no significant correlation between asprosin and thyroid function biomarkers, namely TSH, T3, and T4, whereas asprosin significantly positively

correlated with age. TSH showed no significant difference with all of the measured variables. Moreover, T3 showed a significant negative correlation with age, BMI, and hypertension and a positive significant correlation with T4. In addition, T4 showed significant inverse correlation with smoking and hypertension.

BMI: Body Mass Index, TSH: Thyroid stimulating hormone, T3: Triiodothyronine, T4: Thyroxine

Binary logistic regression analysis

Table 3 shows the results of binary logistic regression as a diagnosis is a dependent variable, and TSH, T3 and T4 are explanatory variables. The current results revealed that the diagnosis of retinopathy is partially (49.1%) predicted by TSH, T3, and T4. Table 3 shows that T3 and T4 are significantly inverse, while T3 is positively associated with a diagnosis of retinopathy.

Table 3: Binary logistic regression analysis with diagnosis as the dependent variable and TSH, T3 and T4 as explanatory variables.

Variables	β	S.E.	Wald	p-value	OR	95%CI
TSH	0.741	0.357	4.312	0.038	2.09	1.04;4.21
T3	-2.41	0.656	13.48	0.000	0.090	0.025;0.325
T4	-0.418	0.169	6.13	0.013	0.658	0.473;0.917

Nagelkerke R^2 =0.491

TSH: Thyroid stimulating hormone, T3: Triiodothyronine, T4: Thyroxine

3. DISCUSSION

The first major finding of the current study is that patients with retinopathy have an unchanged level of asprosin. This is the first study that assessed this glucogenic hormone in diabetic patients. The present study also found that serum levels of asprosin were significantly correlated directly with age. To the best of our knowledge, only one recent study by Atlı et al. reported an elevated asprosin level was found in patients with retinopathy (Atlı, Onalan et al. 2022). High asprosin level is probably a risk factor for the onset of diabetic adverse complications such as diabetic retinopathy (Atlı, Onalan et al. 2022). Studies show that asprosin increases insulin resistance in skeletal muscle by decreasing insulin signaling and enhancing inflammation and endoplasmic reticulum stress (Atli, Onalan et al. 2022, Yardim, Celik et al. 2022). Recent research has shown that hyperglycemic patients have greater asprosin levels than healthy people do, suggesting a link between asprosin and metabolic processes like glucose and lipid metabolism, obesity, and disorders connected to the metabolism (Li, Liao et al. 2018, Bhadel, Shrestha et al. 2020, Zhang, Jiang et al. 2020).

The second major finding of the present study is that we found decreased thyroid hormones, namely T3 and T4 with unchanged TSH levels in patients with retinopathy. Prior studies showed no significant association between TSH and diabetic retinopathy (Qi, Zhang et al. 2017). Multiple processes may be involved in the link between normal thyroid hormone levels and DR in T2DM patients, although the exact nature of this interaction is still unknown (Zou, Li et al. 2020). Maintaining a normal metabolic rate and stable energy levels depend mostly on thyroid function(Bahi, Garnier et al. 2005). Hepatic gluconeogenesis is stimulated by thyroid hormones, which elevate 6-phosphoglucose and glucose transporter 2 in liver cells and hepatic glucose production(Zou, Li et al. 2020). Decreased glucose transport in myocytes and increased insulin resistance in muscle and adipose tissue are two additional effects of thyroid dysfunction(Dimitriadis, Mitrou et al. 2006, Maratou, Hadjidakis et al. 2009). The thyroid hormone is essential for typical human brain development during pregnancy and the first two years of life (Morreale de Escobar, Obregon et al. 2004). Additionally, thyroid hormones have been suggested to contribute to the process of angiogenesis(Carmona-Cortés, Rodríguez-Gómez et al. 2014, Liu, Zheng et al. 2014). Furthermore, subclinical hypothyroidism has been linked to potentially blinding diabetic retinopathy (Yang, Liu et al. 2010).

The current study's third major finding is that abnormal thyroid gland function, as indicated by decreased T3 and T4 did not affect the release of asprosin from adipocytes. Moreover, our results revealed no significant correlation between asprosin and TSH, T3 or T4. Regression analysis of our present results showed that diagnosis of patients, whether retinopathic or not, is significantly explained by T3, T4, which is inversely associated, and TSH with the direct association. In the arteries of diabetic rat, T3 may have an essential role in in relieving diabetic endothelial dysfunction, even though factors including inflammation and endothelial dysfunction are crucial in the evolution of DR (Cai, Manio et al. 2015). Thyroid hormones have a significant role in retinal growth and normal retinal vascular density. In addition, hypothyroidism might facilitate the growth of retinal neovascularization (Yang, Liu et al. 2010). Thyroid hormones also have a role in controlling water metabolism and distribution (Ramis, Artigas et al. 2012). The development of the retina and the rise in retinal vascular density are both influenced by the hypothalamic-pituitary-thyroid axis(Dumitrescu, Liao et al. 2004, Dumitrescu, Liao et al. 2005).

Patients with DR have also shown associations in symptoms among thyroid illness patients. All in all, there is no significant association between thyroid hormones and asprosin level, and the pathophysiology of retinopathy involves thyroid dysfunction without affecting adipocytes function reflected by increased asprosin level.

4. LIMITATIONS

The findings of the present study should be considered while aware of some limitations. First, our study was conducted on a small sample size; thus, more studies with large sample groups should be employed. Second, no control for the effect of treatments on the measured metabolites, so further studies needs to assess the same biomarkers while avoiding major confounders. The current results would be more interesting if we examined the lipid profile, which is influenced by thyroid gland dysfunction and may even explain any variance in the asprosin levels

5. CONCLUSIONS

The current findings indicate that the patients with retinopathy are characterized by hypothyroidism, as reflected by low serum levels of T3 and T4 but normal TSH. Abnormal thyroid function did not impact adipocytes function indicated by normal asprosin level; thus, the pathophysiology of retinopathy probably being partially explained by diminished T3 and T4 with no influence on the asprosin level...

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