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Cardiovascular risk factors in patients with chronic autoimmune thyroiditis

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***Abstract*---**Introduction: Hashimoto's thyroiditis, or chronic autoimmune thyroiditis (CAT), is the most common organ-specific autoimmune disorder. Aim: To determine the relation between thyroid autoimmunity and the presence of cardiovascular risk factors. Patients and Methods: This is a case-control study included fifty patients with autoimmune thyroiditis (case group) and fifty healthy individuals with matched age and sex (control group). We analyzed the levels and variations of thyroid function, lipid profile, high sensitivity C-reactive protein (hs-CRP), insulin resistance markers comprising the HOMA-IR (homeostatic assessment insulin resistance index), QUICKI (quantitative insulin sensitivity check index). Results: There is nonsignificant positive correlation between TSH and LDL, Apo A-I, Lp (a) and Homocysteine while there is nonsignificant negative correlation between TSH and HDL, Apo B, CRP and HOMA-IR. There is a positive significant correlation between FT3 and HDL, HOMA-IR (p=0.024 and 0.013, respectively). Also, there is a significant positive correlation between Anti-Tg and Apo B, Homocysteine (p=0.013 and 0.017, respectively) while there is a significant negative correlation between Anti-Tg and HDL, Lp (a) (p=0.026 and 0.021, respectively). Conclusion: There is an association between thyroid function, thyroid autoimmunity and cardiovascular risk factors, including dyslipidemia, insulin resistance, levels of homocysteine and CRP.

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Introduction

The most frequent type of organ-specific autoimmune disease is Hashimoto's thyroiditis, often known as chronic autoimmune thyroiditis (CAT). Thyroid dysfunction and goitre, as well as a lymphocytic infiltrate throughout the thyroid gland, are hallmarks of thyroiditis ***(Carbotta et al., 2017)***. Cardiovascular disease (CVD) has been linked to hypothyroidism, which in turn has been proven to damage both the left and right ventricles. Hypercholesterolemia, elevated diastolic blood pressure, and heart failure are all manifestations of hypothyroidism. The majority of these alterations may be undone by getting euthyroid status. Even in the absence of an overt thyroid hormone imbalance or after thyroid dysfunction has been remedied, there is indirect evidence that thyroid illness may be related with an elevated vascular risk ***(Ryödi et al., 2018)***. Overt hypothyroidism (OH) has been linked to insulin resistance and dyslipidemia, both of which are associated with cardiovascular disease ***(Purohit & Mathur, 2013)***.

Hemodynamic, hormonal and metabolic abnormalities, as well as C-reactive protein (CRP) and homocysteine variations, all contribute to hypothyroidism's increased risk of cardiovascular disease. In multiple studies, these markers were shown to be elevated in individuals with OH ***(Owecki et al., 2014)***. The relationship between Subclinical hypothyroidism (SCH), lipid profile, insulin resistance and homocysteine level remain disputed, since several research have shown conflicting data ***(Maratou et al., 2009; Chen et al., 2010; Yang et al., 2015)***. Clinical importance may also be difficult to assess since there is debate on the high limit of the reference range for TSH level **(Delitala et al., 2017)**. It's also debatable whether or not individuals benefit from starting treatment while the condition is still in a subclinical stage, since research on the impact of treatment on symptoms and cardiovascular risk in these people has produced conflicting findings ***(Biondi & Cooper, 2008)***. Our study aimed to see whether there was a link between thyroid autoimmunity and cardiovascular risk factors.

Patients and Methods

This is a case-control study carried out at Internal medicine Department, Faculty of Medicine, Menofiya university included fifty patients with autoimmune thyroiditis (case group) and fifty healthy individuals with matched age and sex (control group). All participants provided their informed consent. Institutional ethics committees gave their approval to the research. An autoimmunity was considered to exist when levels of anti-Tg and anti-TPO antibodies were found to be higher than normal in the blood ***(Grani et al., 2015)***.

We excluded patients who were hypertensive, had cardiovascular disease, diabetes mellitus (DM) or were at risk for DM, using thyroid-related medicine or other drug that may interact with our work (drugs used for dyslipidemia, folic acid or vitamin B12 or any hormonal therapy).

All patients had to undergo physical examination. Then their BMI was calculated using a conventional method.

In this study, we focused at the level of thyroid hormones (TSH, FT4, FT3), lipid profiles including total cholesterol (TC), high density lipoprotein (HDL) and low density lipoprotein (LDL), apolipoprotein A-I (Apo A-I), apolipoprotein B (ApoB), lipoprotein (a) [Lp(a)], homocysteine, anti-Tg, anti-TPO (quantitative insulin sensitivity check index). Electrochemiluminescence immunoassay (ECLIA) technique was used to assess thyroid hormones on an Elecsys Analyzer; an immunoluminometric assay was used to quantify TPO-Ab and Tg-Ab (ILMA). All of the blood work was done at the same lab. Additionally, 7.5 and 10 MHz Toshiba Aplio XV transducers were used for thyroid ultrasound examinations.

Statistical analysis:

The data collected were tabulated and analyzed by SPSS (statistical package for social science) version 25 (IBM, Armonk, NY, USA). The following tests were used Paired t-test and Spearman correlation coefficients. P-value was considered significant if < 0.05 and statistically highly significant as P < 0.001.

Results

A total of 100 individuals enrolled in this study, mean $\pm$SD of age in case and control group is 47.25 and 43.81. There is no significance among both groups regarding age and BMI (Table 1). Regarding thyroid function, case group has significant higher values than control group as regard to TSH, Anti-Tg and Anti-TPO ($p < 0.001$) and nonsignificant higher values than control group regarding FT3 (Table 2). Regarding Lipid profile, case group has significant higher levels than control group as regard to TC & LDL ($p < 0.001$) and nonsignificant higher values than control group regarding Lp(a). Also, case group has significant lower values than control group as regard to HDL, Apo A-I and ApoB ($p=0.017$, <0.001 and <0.001, respectively) (Table 3).

Considering insulin sensitivity, case group has significant higher HOMA-IR and lower significant lower QUICKI score than control group ($p <0.001$). There is no significance among both groups regarding Homocysteine and CRP (Table 4). There is nonsignificant positive correlation between TSH and LDL, Apo A-I, Lp (a) and Homocysteine while there is nonsignificant negative correlation between TSH and HDL, Apo B, CRP and HOMA-IR. There is a positive significant correlation between FT3 and HDL, HOMA-IR ($p=0.024$ and 0.013, respectively). Also, there is a significant positive correlation between Anti-Tg and Apo B, Homocysteine ($p=0.013$ and 0.017, respectively**)** while there is a significant negative correlation between Anti-Tg and HDL, Lp (a) ($p=0.026$ and 0.021, respectively) (Table 5).

Table 1: Comparison between groups regarding age and BMI

		Case group (n= 50)	Control group (n= 50)	P value
Age (years)	Mean ±SD	47.25 ±2.47	43.81 ±4.28	0.428
	Range	36 -51	33- 49	
BMI (kg/m2)	Mean ±SD	24.64 ±1.82	26.11 ±1.36	0.251
	Range	22.81- 26.48	23.19 – 27.81	

Table 2: Comparison between groups regarding thyroid function

		Case group (n= 50)	Control group (n= 50)	P value
TSH (µUI/L)	Mean ±SD	6.83	1.43	< 0.001*
	Range	2.73 – 8.42	0.97 – 3.16	
FT3 (ng/mL)	Mean ±SD	2.59	2.51	0.381
	Range	2.26 – 3.41	2.13 – 3.22	
FT4 (µg/mL)	Mean ±SD	0.96	1.04	0.174
	Range	0.91 – 1.36	0.83 – 1.17	
Anti-Tg (IU/mL)	Mean ±SD	127.3	62.8	< 0.001*
	Range	58.2 – 241.6	37.4 – 96.2	
Anti-TPO (IU/mL)	Mean ±SD	729.4	32.8	< 0.001*
	Range	86.4 – 975.1	27.5 – 54.2	

Table 3: Comparison between groups regarding Lipid profile

		Case group (n= 50)	Control group (n= 50)	P value
TC (mg/dL)	Mean ±SD	213	162	< 0.001*
	Range	165 – 229	147 – 203	
HDL (mg/dL)	Mean ±SD	55	78	0.017*
	Range	42 – 65	51 – 83	
LDL (mg/dL)	Mean ±SD	134	98.5	< 0.001*
	Range	102- 159	91 -127	
Apo A-I (mg/dL)	Mean ±SD	102	152	< 0.001*
	Range	98 - 128	124 - 67	
Apo B (mg/dL)	Mean ±SD	94	136	< 0.001*
	Range	91 - 126	125 - 151	
Lp (a) (mg/dL)	Mean ±SD	18.7	13.4	0.133
	Range	6.7 – 64.5	5.2 – 43.3	

TC: total cholesterol; HDL: high density lipoprotein; LDL: low density lipoprotein; Apo A-I: apolipoprotein A-I; Apo B: apolipoprotein B; Lp(a): lipoprotein (a).

Table 4: Comparison between groups regarding insulin sensitivity, Homocysteine and CRP

		Case group (n= 50)	Control group (n= 50)	P value
HOMA-IR	Mean ±SD	3.12	1.84	< 0.001*
	Range	1.82 – 5.27	1.57 – 3.18	
QUICKI	Mean ±SD	0.30	0.44	< 0.001*
	Range	0.25 – 0.42	0.35 – 0.512	
Homocysteine (µmmo/L)	Mean ±SD	7.9	6.1	0.316
	Range	6.5 – 8.2	5.3 – 7.6	
CRP (mg/dL)	Mean ±SD	0.53	0.48	0.125
	Range	0.15-0.61	0.17 – 0.65	

HOMA-IR: homeostatic assessment insulin resistance index; QUICKI: quantitative insulin sensitivity check index; HISI: hepatic insulin sensitivity index; WBISI: whole body insulin sensitivity index; IGI: insulinogenic index; CRP: C-reactive protein.

Table 5: Correlation between thyroid function and other parameters

	Case group (n=50)							
	TSH		**FT3**		**FT4**		**Anti-Tg**	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*
HDL (mg/dL)	- 0.257	0.137	0.417	**0.024***	-0.143	0.329	-0.381	**0.026***
LDL (mg/dL)	0.049	0.725	0.226	0.139	-0.000	0.999	-0.114	0.527
Apo A-I (mg/dL)	0.019	0.932	0.251	0.114	-0.143	0.482	0.137	0.531
Apo B (mg/dL)	-0.004	0.971	-0.038	0.836	0.194	0.245	0.462	**0.013***
Lp (a) (mg/dL)	0.316	0.072	-0.291	0.114	-0.061	0.715	-0.364	**0.021***
CRP (mg/dL)	-0.156	0.421	0.417	0.062	0.044	0.803	0.062	0.791
Homocysteine (µmmo/L)	0.316	0.114	-0.072	0.573	-0.293	0.304	0.426	**0.017***
HOMA-IR	0.012	0.964	0.472	**0.013***	-0.061	0.763	-0.314	0.074

Discussion

Overt hypothyroidism has been linked to CVD, particularly atherosclerosis. Low-density lipoprotein cholesterol, diastolic hypertension, increased coagulability, and effects on vascular smooth muscle are all factors that contribute to atherosclerosis when thyroid hormone levels are reduced ***(Cappola & Ladenson, 2003)***.

In our case group, we found a statistically significant correlation between FT3 level and HDL level. According to prior studies, people with greater FT3 levels may be better protected against CVD ***(O'brien et al., 1997; Nyirenda et al., 2005)***.

Experiments on thyroidectomized rats by ***Ness et al. (1998)*** found that T3 had a beneficial impact on Apo A-I in the hepatic system. These data imply that T3 may have a positive impact on the production of protective apolipoproteins. Activation of Apo A-I seems to be a mechanism by which T3 increases HDL levels in the blood ***(Ritter et al., 2020)***. Because of this, our research shows that when level of FT3 (along with greater levels of TSH) decline, there is also a decline in HDL levels, which increases CVD risk.

As a result of our study, it has been revealed that autoimmunity and especially high level of anti-Tg is correlated with lower HDL. ***Topaloglu et al. (2013)*** also discovered negative correlations between these two measures. We discovered a positive correlation between TSH level and HDL. This is in line with a study that found a long-term drop in HDL cholesterol with an increase in TSH level ***(Asvold et al., 2007)***.

Anti-Tg levels were associated with lower HDL level and higher ApoB level. ApoB is a great part of the LDL particles. These findings show that elevated levels of thyroid autoantibodies are associated with an increased risk of cardiovascular disease. ***Pallas et al. (1991)*** also found a significant relation between dyslipidemia and autoimmune thyroiditis. Also, ***Tamer et al. (2011)*** found that anti-Tg was linked to higher non-HDL cholesterol level.

According to our findings, thyroid autoimmunity may have an impact on lipid profile even if the thyroid is functioning normally. Other authors have made the same argument ***(Mazaheri et al., 2014; Wells et al., 2005)***. Higher levels of interferon-gamma (IFN-γ) may be connected with the independent influence of autoimmunity on lipid profile. Anti-TPO positive euthyroid individuals exhibited greater levels of IFN-γ ***(Mazziotti et al., 2003)***. Furthermore, in HT patients, the Th1 immune response appears to be more prominent than the Th2 responses, and Th1 cells are more likely to release IFN-γ than Th2 cells ***(Roura et al., 1997)***. Foam cell formation, cholesterol absorption, and decreased cholesterol efflux are all influenced by IFN-γ, which causes an imbalance in lipid homeostasis ***(Wang et al., 2002; McLaren et al., 2009)***.

When it comes to insulin resistance, our findings show that TSH is related with greater HOMA-IR values among patients. This is in line with a number of other trials as well ***(Weiss et al., 2005; Vyakaranam et al., 2014)***. We may conclude from these findings that insulin sensitivity reduces when TSH levels rise. Homocysteine levels were found to be elevated in patients with overt hypothyroidism and SCH ***(Maratou et al., 2009; Yang et al., 2015)***. In our work, the levels of FT4 and anti-Tg were shown to be inversely associated to those of homocysteine. According to our findings, elevated TSH level are associated with elevated homocysteine level.

It has been suggested that the inflammation marker C-reactive protein (CRP) is linked to CVD and atherosclerosis. Despite the fact that thyroid hormones and CRP levels had no significant link, ***Christ-Crain et al. (2003)*** discovered that CRP levels rise as thyroid disease progresses. In our study, we discovered a negative association between FT4 and CRP.

Conclusion

This study supports the possible association between thyroid function, thyroid autoimmunity, and CVD risk factors such as dyslipidemia, insulin resistance, homocysteine levels, and high-sensitivity C-reactive protein. In light of these findings, screening and therapy for people with chronic autoimmune thyroiditis may be helpful.

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