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Original article

Nutritional intakes, lipid profile and serum apo-lipoproteins concentrations and their relationship with antithyroid, antigliadin and anti-tissue transglutaminase antibodies in patients with Hashimoto's thyroiditis

*Shaghayegh Hadizadeh Riseh[1], Majid Mobasseri[2], Mohammad-Asghari Jafarabadi[3], Mahdieh Abbasalizad Farhangi[*4], Elham Ajorlou[5]*

[1]Student Research Committee, Tabriz University of Medical Sciences, Tabriz, Iran; [2]Department of Endocrine and Metabolism, Emam Reza Teaching Hospital, Medicine Faculty, Tabriz University of Medical Sciences, Tabriz, Iran; [3]Road Traffic Injury Research Center, Tabriz University of Medical Sciences, Tabriz, Iran; [4]Nutrition Research Center, Department of Community Nutrition, School of Nutrition, Tabriz University of Medical Sciences, Tabriz, Iran - E-mail: abbasalizad_m@yahoo.com; [5]Drug Applied Research Center, Department of Medical Nanotechnology, Faculty of Advanced Medical Science, Tabriz, Iran

Summary. *Background and aim:* Hashimoto's thyroiditis (HT) is the most common autoimmune thyroid disease and it is in coexistence with many autoimmune disorders, especially celiac disease. The present study is the first to evaluate nutritional intakes in Hashimoto's thyroiditis patients and the relationship between nutritional intakes and metabolic factors with anti-thyroid, anti-gliadin and anti-tissue transglutaminase antibodies in patients with Hashimoto's thyroiditis. *Methods:* This study was performed on 82 women aged 20-50 years including 40 patients with Hashimoto's thyroiditis and 42 healthy age-matched individuals. Dietary intakes were assessed using a semi- quantitative food-frequency questionnaire (FFQ). Physical activity was obtained by metabolic equivalent (MET) questionnaire. Anthropometric assessments were performed and biochemical assays including thyroid hormones, antithyroid antibodies, anti-tissue transglutaminase and anti-gliadin antibodies, lipid profile and apo-lipoprotein were measured. *Results:* Serum lipids and apo-liporotein concentrations were higher in patients with Hashimoto's thyroiditis compared with healthy control group. Moreover these patients had a significantly lower consumption of antioxidants including vitamin E or selenium compared with healthy individuals ($P < 0.05$). Nutritional intakes and metabolic factor also positively associated with anti-tissue transglutaminase and anti-gliadin antibodies in patients with Hashimoto's thyroiditis ($P < 0.05$). *Conclusion:* Patients with Hashimoto's thyroiditis had higher metabolic abnormalities and lower intakes of antioxidant including vitamin E and selenium. Moreover significant positive relations were also identified between nutritional parameters and metabolic factors with anti-thyroid, anti-gliadin or anti-tissue transglutaminase antibodies in these patients. Further researches are needed to better clarify these relationships and underlying mechanisms.

Keywords: Hashimoto's thyroiditis, nutrition, apo-lipoprotein

Introduction

Hashimoto's thyroiditis (HT) as the most prevalent autoimmune thyroid disease, is characterized by appearance of hypothyroidism or goiter and presence of high serum concentrations of thyroid antibodies like anti-thyroid peroxidase (TPO-Ab) and anti-thyroglobulin (TG-Ab) antibodies (1-4). Hashimoto's thyroiditis is in coexistence of several other autoimmune diseases like type 1 diabetes mellitus, vitiligo, Addison's disease and specially celiac disease (5, 6). Based on large epidemiological surveys, Hashimoto's

thyroiditis is the most frequent reason of hypothyroidism in 4% to 9.5% of the adult population (7, 8).

Numerous environmental factors like infection, stress, smoking could affect thyroid function; among them several reports highlighted the role of diet and its composition in disease initiation and progression; evidences indicated the role of several micronutrient deficiencies such as iodine, iron, selenium and zinc in etiology of thyroid disorders (1, 9-11). Additionally several studies revealed the relationship between macronutrient intakes and thyroid hormones; Pasquali et al. (12) and Mathieson et al. (13) reported that lower dietary carbohydrate content had an influence on the magnitude of fall in serum T3 levels in obese patients. Smallridge et al. also showed that low protein diet leads to elevation in serum total T3 in rats (14). However no report of the relationship between nutritional intakes of macro and micronutrients in patients with Hashimoto's thyroiditis was found; on the other hand, Hashimoto's thyroiditis is associated with major disturbances in serum lipids and increases in serum atherogenic apo-lipoprotein (15, 16) which might be modified by special nutritional regimens; since celiac is the most prevalent autoimmune disorder in Hashimoto's thyroiditis and dietary factors like gluten and gliadin in grains and cereals can trigger the progression of disease (5, 17) therefore one can assume that dietary factors could also affect the Hashimoto's thyroiditis progression via their indirect effect on celiac related auto-antibodies including anti-gliadin (AGA) and anti-tissue transglutaminase (ATA); therefore in the current case-control study we aimed to compare intakes of energy, macro and micronutrients in patients with Hashimoto's thyroiditis and healthy individuals and also to evaluate the relationship between nutritional intakes and metabolic factors with anti-thyroid, anti-gliadin and anti-tissue transglutaminase antibodies in patients with Hashimoto's thyroiditis.

Materials and Methods

Subjects

This case-control study included 40 patients with Hashimoto's thyroiditis and 42 healthy age-matched volunteer subjects. All patients were recruited from the outpatient clinics of Tabriz University of Medical Sciences. Patients were excluded if they had a history of celiac disease, gastrointestinal disorders, diabetes, cardiovascular disease, thyroid surgery, pregnancy and lactation or were using drugs that could interfere with thyroid function including anti-diabetic medications, corticosteroids, amiodarone, phenytoin, statins, aspirin and being on any dietary restriction programs such as gluten free or weight loss diets for at least 3 months prior participation in study. The study was approved by the ethics committee of Tabriz University of Medical Sciences (Registration code: 5/4/1700) and written informed consent was obtained from all participants prior participation in the study.

Anthropometric measurement

Weight was measured in light clothing without shoes using a calibrate scale (SECA, Hamburg, Germany) to the nearest 0.1 kg and height was measured to the nearest 0.1 cm without shoes using a non-stretchable measurement tape. BMI was calculated as weight (kg) divided by height squared (m^2). Waist circumference (WC) was recorded as the smallest measurement between the iliac crest and the lateral costal margin and hip circumference (HC) was the largest measurement over the buttocks, using a non-elastic tape. Waist to hip ratio (WHR) was then calculated as WC divided by HC.

Physical activity was determined by the questionnaire in which nine different metabolic equivalent (MET) levels were ranged on a scale from sleep/rest (0.9 METs) to high intensity physical activities (> 6 METs). This questionnaire had previously been modified and validated among Iranian people and also was found to be significantly associated with the findings of International Physical Activity Questionnaire (IPAQ) (18). For each activity, the METs value was multiplied by the time spent at that particular level and the MET- time at each level was added to obtain a total over 24 hours MET-time, representing the physical activity level on an average weekday. Physical activities of different intensities were categorized to sedentary (<3 METs), moderate (3–6 METs) and vigorous (> 6 METs) respectively.

Biochemical analysis

Venous blood samples were obtained from all of participants after an overnight fasting period. The blood samples were then centrifuged at 3000×g for 10 minutes; sera samples were extracted and stored at −70°C until biochemical assays. Serum thyroid-stimulating hormone (TSH), triiodothyronine (T3), thyroxine (T4) concentrations were analyzed by enzyme linked immunosorbent assay (ELISA Kit, Pishtaz Tebe Co., Tehran, Iran). Serum anti thyroid peroxidase, anti-thyroglobulin, anti-gliadin and anti-tissue transglutaminase antibodies were measured by the commercially available solid-phase ELISA kits (AESKULISA, Wendelsheim, Germany).

Serum total cholesterol (TC), triglyceride (TG), high density lipoprotein cholesterol (HDL-C), apo-lipoprotein AI (Apo AI) and apo-lipoprotein B (Apo B) concentrations were determined by Abbott ALCYON ™ 300 auto-analyzer using kits (Pars-Azmoon, Tehran, Iran). Low density lipoprotein cholesterol (LDL-C) values were calculated using the Friedewald formula (19).

Assessment of dietary intake

Daily dietary intakes were assessed using a 168-item interviewer-administered semi quantitative food-frequency questionnaire (FFQ) (20). The questionnaire consisted of a list of foods with a standard serving size commonly consumed by Iranian people. Participants reported the frequency of consumption of each food item during the previous year on a daily, weekly, monthly, yearly or never basis. Ultimately data analysis was obtained by Nutritionist IV software.

Statistical analysis

Statistical calculations were performed using the SPSS version 16.0 software (SPSS Inc., Chicago, IL, USA). A kolmogorov-Smirnov test was used to test normality of data distribution. Independent sample T-test and Mann–Whitney U-test were used to compare continuous variables between two groups when appropriate. Chi square test was used to compare categorical variables. Pearson's correlation or Spearman's rank correlation tests were used to identify associations. Partial correlation analysis was performed to test the association between parameters with adjustment for confounding variables. Continuous variables are presented as means (SD) or median (25^{th}- 75^{th} percentiles) and categorical variables as number and percentage. Results were considered significant when P <0.05.

Results

The demographic and anthropometric parameters of study subjects are shown in Table 1. No significant difference was observed in age, BMI or physical activity level between participants. Table 2 presents the comparison of biochemical variables between groups. Serum TSH, anti-TPO, anti-TG and Apo AI concentrations were significantly higher and serum T3 concentrations was significantly lower in Hashimoto' thyroiditis patients compared with control group (P < 0.05). Serum concentration of IgA-ATA, IgG-ATA, TC, LDL-C and HDL-C were also higher in case group compared with control group however no significant threshold has been achieved. There was also a positive relationship between IgA-ATA and IgA-AGA with anthropometric indices in patients and not in control group (Figure 1). Significantly lower dietary intakes of vitamin E and selenium in patients were also reported (Table 3, P < 0.05). Protein and carbohydrate intake were positively associated with IgA-

Table 1. Subject characteristics

Variable	HT (n=40)	Control (n=42)	P†
Age (years)	34.38 (9.39)	33.93 (7.55)	0.813
BMI (kg/m²)	24.85 (5.20)	26.43 (6.17)	0.217
WC (cm)	83.14 (12.52)	86.66 (12.62)	0.209
Physical activity (Kcal/min/week)			
MET: 3-6	33 (82.5)	34 (81)	0.856
MET > 6	7 (17.5)	8 (19)	

HT, Hashimoto's thyroiditis; BMI, Body Mass Index; WC, waist circumference, MET, metabolic equivalent; †P for Physical activity based on Chi-Square Tests, otherwise based on Independent sample T-test. Data are presented as mean ± SD or number (percent)

Table 2. The comparison of biochemical variables between study groups

Variable	HT (n=40)	Control (n=42)	P†
TSH (mIU/l)	3.65 (1.10 to 6.02)	1.95 (1.17 to 2.50)	**0.032**
T3 (nmol/L)	1.30 (1 to 1.40)	1.40 (1.20 to 1.60)	**0.024**
T4 (nmol/L)	7.15 (6.40 to 7.50)	7.00 (6.77 to 7.30)	0.993
Anti-TPO (IU/ml)	894.35 (187.60 to 1.408)	13.45 (9.65 to 24.77)	**< 0.001**
Anti-TG (IU/ml)	62.00 (14.90 to 338.87)	9.85 (8.50 to 18.00)	**< 0.001**
IgG-ATA (U/ml)	4.90 (1.97 to 8.22)	3.05 (1.90 to 6.95)	0.305
IgA-ATA (U/ml)	5.35 (2.55 to 15.82)	4.55 (2.70 to 10.60)	0.904
IgA-AGA (U/ml)	5.55 (2.55 to 11.85)	6.00 (3.77 to 12.22)	0.464
IgG-AGA (U/ml)	2.50 (1.82 to 7.77)	4.70 (2.47 to 6.42)	0.152
TC (mmol/L)	174.25 (36.22)	163.88 (31.04)	0.167
TG (mmol/L)	78 (55.25 to 1.11)	80.5 (59.75 to 1.37)	0.690
LDL-C (mmol/L)	94.24 (40.70)	90.53 (27.40)	0.629
HDL-C (mmol/L)	61.20 (24.69)	53.40 (10.05)	0.063
Apo-B (µg/ml)	107.10 (19.85)	101.66 (20.28)	0.224
Apo-AI (µg/ml)	211.62 (33.73)	192.57 (30.93)	**0.009**

HT, Hashimoto's thyroiditis; TSH, thyroid stimulating hormone; T3, triidothyronie; T4, thyroxine; anti-TPO, anti-thyroid peroxidase antibody; anti-TG, anti-thyroglobulin antibody; IgG and IgA-ATA, IgG and IgA anti-tissue transglutaminase antibodies; IgA and IgG-AGA, IgA and IgG anti-gliadin antibodies; TC, total cholesterol; TG, triglyceride; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; Apo-B, apo-lipoprotein B; Apo-AI, apo-lipoprotein AI. †P based on Independent sample T-test or Mann–Whitney U test. Data are presented as mean ± SD or medians (25th percentile –75th percentile)

ATA in case group but not in control group (Figure 2). Significant positive relations were also identified between thyroid hormones and serum lipids and apo-lipoprotein concentrations which remained significant even after adjusting for confounding effects of physical activity and BMI (Table 4).

Discussion

In the current case-control study, we demonstrated a higher level of apo-lipoproteins, lipid profile and their positive association with thyroid hormones in patient with Hashimoto's thyroiditis. We also observed a significantly lower consumption of antioxidants including vitamin E or selenium in these patients compared with healthy controls. To our knowledge this is the first study evaluated the relationship between nutritional intakes and metabolic factors with anti-thyroid, anti-gliadin and anti-tissue transglutaminase antibodies in patients with Hashimoto's thyroiditis.

Dietary components are significant predictors of thyroid hormone metabolism; total energy, carbohydrates, and several micronutrients including iodine, selenium and iron can affect thyroid hormone status. In the current study, patients with Hashimoto's thyroiditis had significantly lower intakes of antioxidants including vitamin E and selenium compared with control group (P< 0.05). Several interventional trials have indicated the positive therapeutic effects of selenium supplementation in autoimmune thyroid disease (21-23). Toulis et al. (24) and Mazokopakis et al. (25) also reported a significant reduction of serum anti-TPO antibody after selenium supplementation in Hashimoto's thyroiditis patients. Several experimental studies have also indicated that hypothyroidism is accompanied with increased oxidative stress and revealed beneficial effects of vitamin E in protection of the organism against oxidative stress (26, 27).

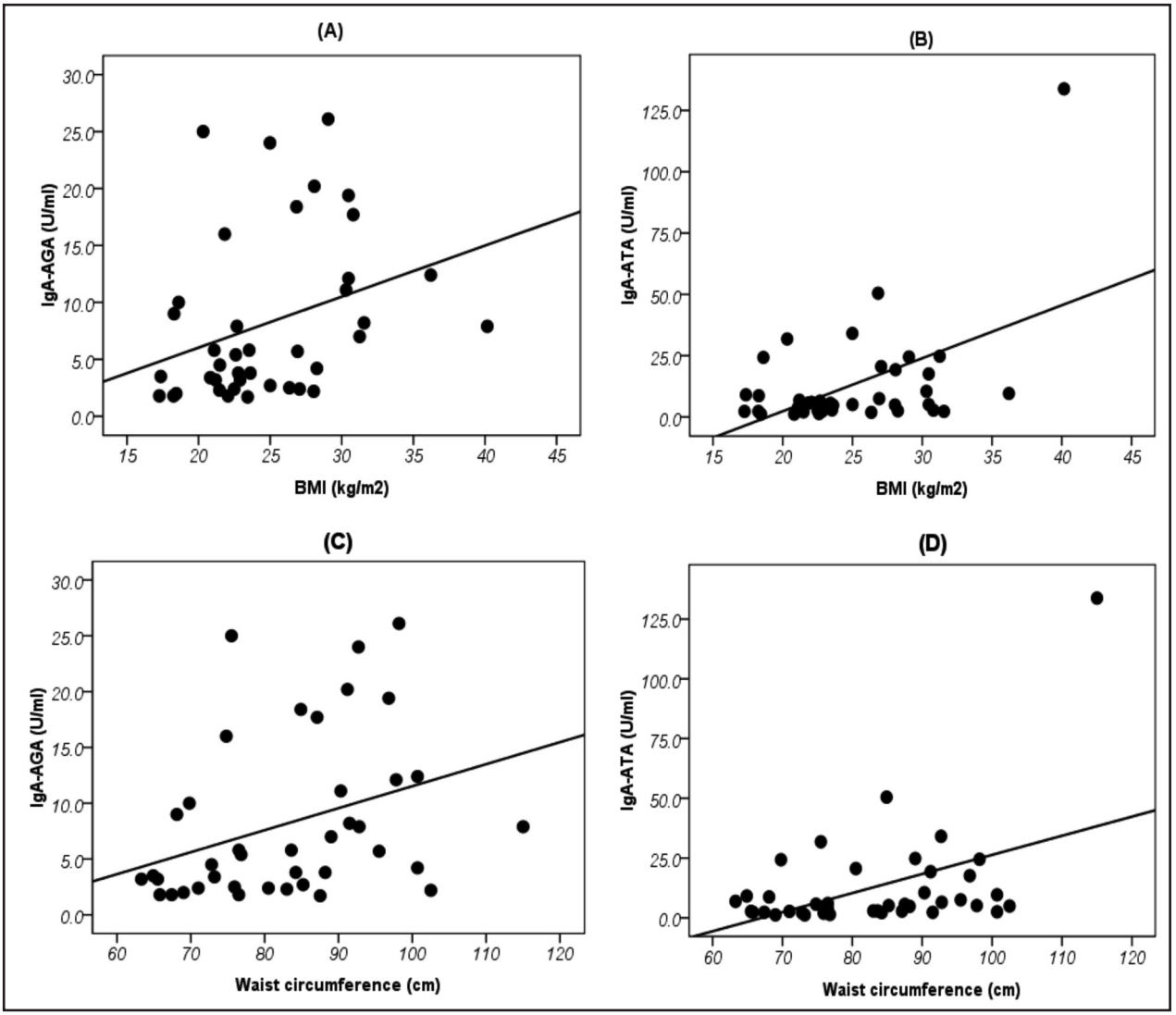

Figure 1. Relation of anthropometric indices with IgA-anti tissue transglutaminase and IgA-anti gliadine antibodies in Hashimoto's thyroiditis patients (A: r=0.324 P=0.041; B: r=0.500 P=0.001; C: r=0.343 P=0.030; D: r=0.445 P=0.004)

We also observed a positive relationship between dietary carbohydrate and protein intake with anti-tissue transglutaminase as a celiac related antibody in patients with Hashimoto's thyroiditis. Numerous studies have indicated the coexistence of Hashimoto's thyroiditis with celiac disease (5, 28). Moreover some studies reported that high prevalence of positive diagnostic markers of celiac disease e.g. anti-tissue transglutaminase antibody titers in patients with autoimmune thyroid disease especially Hashimoto's thyroiditis (29). Ventura et al. reported the duration of exposure to gluten plays a pivotal role in the development of autoimmune disorders as autoimmune thyroid disease in patients with celiac disease (30). Furthermore Toscano et al. (31) and Sategna-Guidetti et al. (32) reported gluten free diet can improve thyroid function and reduce thyroid antibodies' concentration in patients with celiac disease. It was also noted, anti-tissue transglutaminase and anti-gliadin antibodies will be reduced with the elimination of gluten from diet in patients with celiac disease (33). Although we did not evaluate gluten intake in our participants but positive relationships between anti-tissue transglutaminase and protein or carbohydrate intake suggests that higher in-

Table 3. Comparison of energy, macro and micronutrient intakes between study groups

Variable	HT (n=40)	Control (n=42)	P†
Calories (kcal)	2560.32 (688.41)	2670.66 (554.13)	0.425
Protein (gr)	79.45 (23.92)	85.25 (22.38)	0.260
Carbohydrate (gr)	387.83 (114.92)	406.49 (95.11)	0.425
Fat total (gr)	82.09 (42.16)	83.02 (30.92)	0.909
Vit C (mg/day)	169.77 (89.92)	160.47 (80.49)	0.633
Vit E (mg/day)	3.40 (2.89 to 5.17)	4.51 (3.26 to 7.13)	**0.036**
Iron (mg/day)	17.26 (5.32)	17.85 (3.79)	0.561
Zinc (mg/day)	7.75 (2.71)	8.45 (2.72)	0.253
Selenium (mg/day)	0.099 (0.030)	0.12 (0.04)	**0.015**
Chromium (mg/day)	0.036 (0.010)	0.038 (0.014)	0.535
Sodium (mg/day)	1330.31 (634.06)	1391.80 (493.65)	0.625
Potassium (mg/day)	3600.47 (1279.63)	3614.33 (1188.58)	0.960
Dietary Fiber (gr)	19.43 (7.02)	19.81 (6.45)	0.799
PUFA (gr)	19.62 (13.54 to 27.96)	22.54 (11.99 to 28.48)	0.636

HT, Hashimoto's thyroiditis; PUFA, polyunsaturated fatty acids. †P based on Independent sample T-test or Mann–Whitney U test. Data are presented as mean ± SD or medians (25th percentile –75th percentile)

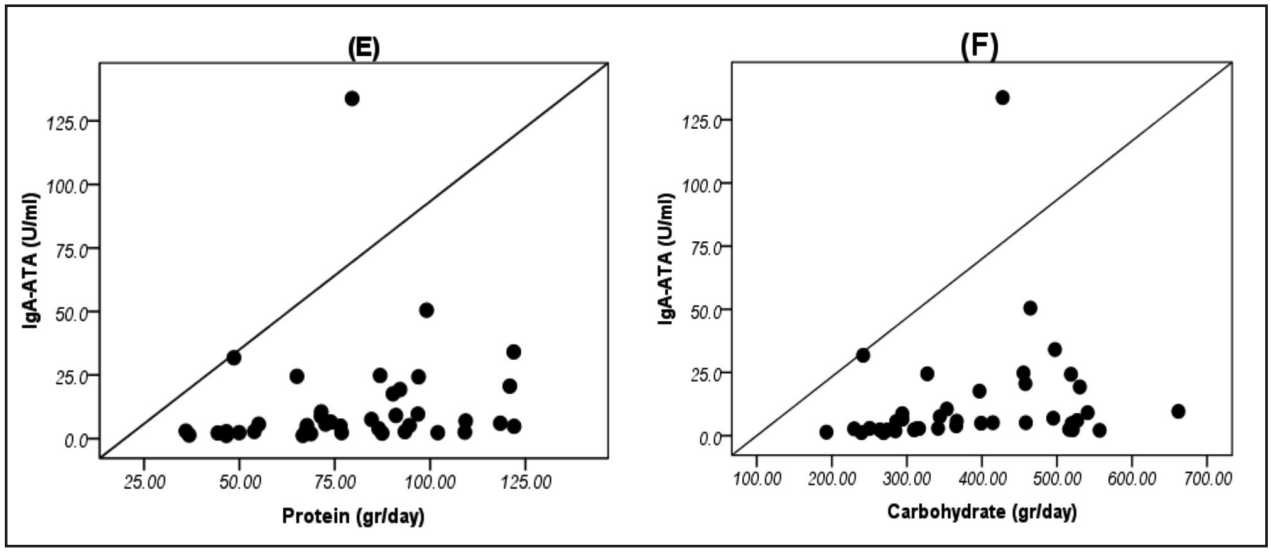

Figure 2. Relation of protein and carbohydrate intake with IgA-anti tissue transglutaminase antibody in Hashimoto's thyroiditis patients (E: r=0.395 P=0.012; F: r=0.411 P=0.008).

take of these macronutrients might trigger the disease progression.

In the current study higher concentrations of Apo B and Apo AI were observed in patients with Hashimoto's thyroiditis. Several lipids were also non-significantly higher in these patients. Likewise serum TSH was positively correlated with serum TC, HDL-C, LDL-C and Apo B concentrations. Consistent with

Table 4. Correlation analyses between T4, TSH and lipid parameters before and after adjusting for BMI and physical activity in Hashimoto's thyroiditis patients

	Before adjustment		After adjustment	
	T4 (nmol/L)	**TSH (mIU/l)**	**T4 (nmol/L)**	**TSH (mIU/l)**
HDL-C (mmol/L)	-0.286	0.325*	0.012	0.124
LDL-C (mmol/L)	-0.258	0.351*	-0.253	0.286
TC (mmol/L)	-0.346*	0.486**	-0.347*	0.451**
TG (mmol/L)	-0.034	0.206	-0.288	0.172
Apo B (µg/ml)	-0.209	0.460**	-0.272	0.497**

*T4, thyroxine; TSH, thyroid stimulating hormone; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride; Apo-B, apo-lipoprotein B. Numbers represent r values (correlation coefficients) between the parameters. *P<0.05, **P<0.01.*

our findings, Caraccio et al (34) reported higher concentrations of serum lipids and Apo B in patients with Hashimoto's thyroiditis and their significant positive association with serum TSH concentrations. Lee et al also reported a negative association between serum T4 concentrations, serum lipids and Apo B in patients with autoimmune thyroid disease ($P < 0.05$) (35).

These findings further highlights the association between Hashimoto's thyroiditis and coronary heart disease via their possible mechanisms in inducing lipid abnormalities or even change in anthropometric measurements by alterations in adiposity as confirmed in the current study and our previous researches (15, 36-38). These alterations might be attributed to increased cholesterol synthesis and decreased hepatic and lipoprotein lipases activity (39). Moreover, decreased cholesterol excretion, reduced number of LDL receptors on the hepatic cell surface and decreased plasma LDL receptors could also responsible to lipid abnormalities in hypothyroidism (40).

Conclusion

Our study highlights that patients with Hashimoto's thyroiditis had higher lipid profile and apo-lipoprotein concentrations and lower intakes of vitamin E and selenium compared with healthy control subjects. Moreover, to our review of literature this is the first report evaluated the nutritional intakes in patients with Hashimoto's thyroiditis and the relationship between nutritional intakes and metabolic factors with anti-thyroid, anti-gliadin and anti-tissue transglutaminase antibodies in these patients. Further descriptive and interventional studies are needed to evaluate dietary habits and clarify the role of dietary modifications as therapeutic approaches in disease attenuation.

Authorship

We thank all of the participants in the current study. We also thank Nutrition Research Center for providing laboratory facilities. Hereby we confirm that each coauthor participated in the work sufficiently and the authorship is as follows: Hadizadeh Riseh Sh was participate in data collection, data analysis and wrote the first draft of the paper, Farhangi MA was involved in the conception and designing, supervising the project and revision of the manuscript and Mobasseri M was involved in patients recruitment and disease diagnosis. Ajorlou E was involved in laboratory analysis.

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Correspondence:
Mahdieh Abbasalizad Farhangi
Nutrition Research Center, Department of Community Nutrition, School of Nutrition, Tabriz University of Medical Sciences, Tabriz, Iran.
Tel: +413 335 7584
Fax: +413 335 7581
E-mail: abbasalizad_m@yahoo.com