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RESEARCH ARTICLE

RETROSPECTIVE EVALUATION OF RISK FACTORS FOR ISCHEMIC HEART DISEASE IN PATIENTS WITH DERMATITIS HERPETIFORMIS

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ABSTRACT

Purpose: Some have proposed that the cardiovascular risk among individuals with dermatitis herpetiformis (DH) differs from that of the general population. This study aimed to analyze cardiovascular risk factors in DH patients and compare them to a matched control group without DH or celiac disease.
Material and Methods: This was a retrospective hospital-based study involving patients diagnosed with DH, both clinically and histopathologically, along with age- and sex-matched control subjects without the disease. The presence of ischemic heart disease, and the risk factors including laboratory values, treatment and comorbidity histories were evaluated comparatively (SPSS version 29.0).
Results: Thirty-five patients with DH and 49 controls were included. No significant difference was found between the DH patients and controls regarding the prevalence of ischemic heart disease (22.9% vs. 14.3%, p: 0.312). Diabetes mellitus was significantly higher and HDL cholesterol levels were significantly lower in the DH group (respectively, p: 0.044 and p: 0.018). Celiac autoantibodies, the laboratory values, or treatments did not show any significant correlation with heart disease in DH.
Conclusion: This study revealed that HDL cholesterol were significantly lower in DH patients compared to general population. More research is needed to optimize the cardiovascular health of DH patients

Keywords: Dermatitis herpetiformis, ischemic heart disease, cardiovascular disease, risk factors

INTRODUCTION

Dermatitis herpetiformis (DH) is a rare disorder featuring severe pruritic inflammatory vesicles and papules on skin. This autoimmune cutaneous disorder is considered to be related with gluten sensitivity. Most patients with cutaneous disease (dermatitis herpetiformis) have also celiac disease (enteropathy). Enteropathy in these patients is mostly asymptomatic or minimally symptomatic (1).

Some researches have noted that celiac disease is associated with increased cardiovascular risk, including stroke, ischemic heart disease, and thromboembolic complications. However, the evidence is inconsistent (2, 3). In addition, many

studies have shown increased mortality in celiac patients (3, 4).

On the other hand, mortality studies in DH are limited and have been associated with lower mortality rates than in the population (3). More data on the relationship between cardiovascular diseases and DH are needed. Some have proposed that the rate of cardiovascular disease in these patients differs from that of the general population due to differences in cardiovascular risk factors such as lipid profile (5).

The purpose of the present study was to compare cardiovascular disease risk factors in patients with DH with a matched control cohort without DH or celiac disease. In addition, it was aimed to compare these risk factors between those with and without cardiovascular disease in the patient group with DH.

MATERIAL AND METHODS

This retrospective hospital-based study aimed to assess ischemic heart disease risk factors in patients with DH and matched control subjects without DH. The study was approved by Dokuz Eylül University Noninvasive Clinical Studies Ethics Committee (Date: 19.07.2023, Decision No: 2023/23-08). It included all patients diagnosed with DH clinically and histopathologically at Dokuz Eylül University Hospital Dermatology Clinic between 2000 and 2023. The control group comprised patients without DH, admitted to our hospital outpatient clinics during the same period, matched in terms of age and gender, and consecutively enrolled in the study. Patients with unavailable data or unclear diagnoses were excluded from the study.

Demographic data and data on risk factors of ischemic heart disease in DH patients and controls were collected from the hospital's electronic data recording system. The patient's anamnesis notes, laboratory values examined by our clinic during patient follow-up, and ICD codes in the patient file for comorbidities matching ischemic heart disease, hypertension, and diabetes mellitus were recorded. Risk factors examined retrospectively included protein in urine, glucose in urine, LDL cholesterol, HDL cholesterol, triglycerides, CRP levels, fasting glucose. Celiac disease antibodies, treatment history, and signs of malabsorption (deficiency in at least one of iron, folate, calcium, vitamin D or hemoglobin) were also evaluated.

Statistical analyses

The analysis of the data involved using t-tests and Mann-Whitney U tests for comparing numerical parameters. For categorical variables, we employed the Pearson chi-square test and Fisher's exact test. All statistical analyses were conducted using SPSS software version 29.0.

RESULTS

A total of 84 participants, 35 with DH and 49 in the control group, were included in our study. Age, sex,

Table 1. Basic Characteristics of the Patient and Control Group

		DH Patients (n=35)		Control Group (n=49)		All participants (n=84)		
		Mean ± SD or n	Median (min-max) or %	Mean ± SD or n	Median (min-max) or %	Mean ± SD or n	Median (min-max) or %	p values
Age, years		52.77 ± 16.96	52 (23 - 89)	57.9 ± 14.92	57 (21 - 89)	55.76 ± 15.91	54.5 (21 - 89)	0.137[1]
Sex	**Female**	20	57.10%	31	63.30%	51	60.70%	0.571[2]
	Male	15	42.90%	18	36.70%	33	39.30%	
Smoking		8	22.90%	9	18.40%	17	20.20%	0.671[2]
Family History of Ischemic Heart Disease		2	5.70%	2	4.10%	4	4.80%	0.729[2]
Family History of Celiac Disease		0	0.00%	0	0.00%	0	0.00%	N/A[2]

Abbreviations; DH: Dermatitis Herpetiformis, SD: standard deviation. N/A: Non-applicable.

[1]Mann-Whitney u test was used, [2]Pearson chi-square test was used

Table 2. Evaluation of ischemic heart disease and related risk factors in DH patients and Control group

	DH Patients (n=35)		Control Group (n=49)		
	n	%	n	%	p values
Ischemic Heart Disease	8	22.90%	7	14.30%	0.312
Hypertension	11	31.40%	21	42.90%	0.288
Diabetes Mellitus	14	40.00%	10	20.40%	**0.044****
Protein in Urine	2	5.70%	5	10.20%	0.463
Glucose in Urine	2	5.70%	2	4.10%	0.729

Abbreviations; DH: Dermatitis Herpetiformis. Pearson chi-square test was used. Significant p values were shown in bold and with double star superscript (**) sign.

Table 3. Comparison of laboratory parameters between DH patients and Control Group

	DH Patients (n=35)		Control Group (n=49)		p values
	Mean ± SD	Median (min-max)	Mean ± SD	Median (min-max)	
LDL cholesterol, mg/dL	122 ± 29.97	118 (73 - 206)	121.41 ± 25.32	119 (72 - 178)	0.863
HDL cholesterol, mg/dL	46.14 ± 10.54	45 (26 - 71)	53.33 ± 15.34	55 (22 - 86)	**0.018****
Triglyceride, mg/dL	155.71 ± 151.8	121 (42 - 927)	133.12 ± 64.81	117 (58 - 376)	0.885
CRP levels, mg/dL	4.6 ± 4.45	2.5 (0 - 15)	4.1 ± 3.58	3 (0 - 14)	0.972
Fasting Glucose, mg/dL	106.34 ± 33.71	99 (74 - 254)	101.13 ± 31.32	93 (76 - 269)	0.348

Abbreviations; DH: Dermatitis Herpetiformis, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, CRP: C-Reactive Protein, SD: standard deviation. Mann-Whitney U test was used. Significant p values were shown in bold and with double star superscript (**) sign.

smoking history, and ischemic heart disease in family members were similar in DH and control groups. None of our participants had a family history of celiac disease (Table 1).

The prevalence of ischemic heart disease was 22.9% (8/35) in DH patients and 14.3% (7/49) in the control group (p:0.312). Although there was no significant difference between the two groups, parameters that have the potential to predict ischemic heart disease in DH patients were tested. Accordingly, the presence of hypertension, protein in the urine, and glucose in the urine were similar in DH patients and control group (all p>0.05) (Table 2). The prevalence of diabetes mellitus (DM) was significantly higher in DH patients (20.4% vs. 40%, p:0.044) (Table 2).

HDL cholesterol levels, which are protective against ischemic heart disease, were significantly lower in DH patients (p: 0.018). LDL cholesterol levels, triglyceride, CRP, and fasting glucose levels were also similar between the DH group and the control group (p: 0.863, p: 0.885, p: 0.972, and p: 0.348, respectively) (Table 3).

The prevalence of celiac presence was 37.1% (13/35) in DH group. 28.6% of DH patients were followed without treatment, but the most commonly used treatment was dapsone (11/35, 31.4%). Antiendomysium-IgA positivity was 22.9% (8/35), antigliadin-IgA positivity was 28.6% (10/35), anti-tissue transglutaminase IgA positivity was 20% (7/35) and tissue transglutaminase IgG positivity was 5.7% (2/35) in DH patients.

The occurrence of ischemic heart disease was notably greater among male DH patients compared to females (p: 0.36). Again, the prevalence of ischemic

Table 4. Comparison of basic demographic and comorbidity parameters between DH patients with and without ischemic heart disease

		DH patients without IHD (n=27)		DH patients with IHD (n=8)		
		n	**%**	**n**	**%**	**p values**
Sex	**Female**	18	66.70%	2	25.00%	**0.036****
	Male	9	33.30%	6	75.00%	
Smoking		5	18.50%	3	37.50%	0.261
Family History of Ischemic Heart Disease		2	7.40%	0	0.00%	0.428
Hypertension		7	25.90%	4	50.00%	0.198
Diabetes Mellitus		11	40.70%	3	37.50%	0.869
Signs of Malabsorption		6	22.20%	2	25.00%	0.869
Protein in Urine		1	3.70%	1	12.50%	0.346
Glucose in Urine		2	7.40%	0	0.00%	0.428
Celiac Disease		10	37.00%	3	37.50%	0.981
Treatment	**Dapsone**	8	29.60%	2	25.00%	0.928
	NB-UVB	1	3.70%	0	0.00%	
	Dapsone + NB-UVB	1	3.70%	0	0.00%	
	Fexofenadine Hydrochloride	2	7.40%	1	12.50%	
	No treatment	15	55.60%	5	62.5%	
Anti-Endomysium IgA Positive		6	22.20%	2	25.00%	0.869
Anti-Gliadin IgA Positive		8	29.60%	2	25.00%	0.799
Anti-Tissue Transglutaminase IgA Positive		6	22.20%	1	12.50%	0.867
Tissue Transglutaminase IgG Positive		2	7.40%	0	0.00%	0.648

Abbreviations; DH: Dermatitis Herpetiformis, IHD: Ischemic Heart Disease, IgA: Immunoglobulin A, IgG: Immunoglobulin G, NB-UVB: Narrowband Ultraviolet B. Pearson Chi-Square test was used. Significant p values were shown in bold and with double star superscript (**) sign.

heart disease was significantly higher in older DH patients (p: 0.034). There was no significant relationship between ischemic heart disease and other factors investigated such as smoking, family history of heart disease, presence of hypertension, presence of DM, presence of malabsorption findings, protein positivity in urine, presence of glucose in the urine, presence of celiac diagnosis, treatment received, anti-endomysium IgA positivity, anti-gliadin IgA positivity, anti-tissue transglutaminase IgA positivity and tissue transglutaminase IgG positivity in DH patients (Table 4). Laboratory parameters, including LDL, HDL, triglyceride levels, CRP, and fasting glucose levels, did not exhibit a significant association with the development of ischemic heart disease in DH patients (Table 5).

DISCUSSION

This study demonstrated that there was no significant difference in the occurrence of ischemic heart disease between the group of DH patients and the matched control group, with similar age, sex, smoking habits, and a family history of ischemic heart disease. Consistently, in a study with large cohorts diagnosed with DH and celiac disease, it was observed that the risk of cardiovascular disease was elevated in those with celiac disease, while no such increase was evident in patients with DH (aHR 1,16; 95% GA 0,91–

Table 5. Comparison of age and laboratory parameters between DH patients with and without ischemic heart disease

	DH patients without IHD (n=27)		DH patients with IHD (n=8)		p values
	Mean ± SD	Median (min-max)	Mean ± SD	Median (min-max)	
Age at diagnosis, years	49.5 ± 15.7	47 (23 – 84)	63.9 ± 17.3	65 (30 – 89)	**0.034****
LDL cholesterol, mg/dL	119.8 ± 29.7	113 (74 – 206)	129.5 ± 31.5	137 (73 – 167)	0.323
HDL cholesterol, mg/dL	47.6 ± 10.9	46 (26 – 71)	41.3 ± 7.9	38.5 (33 – 54)	0.104
Triglyceride, mg/dL	152 ± 162.6	121 (43 – 927)	168.4 ± 116.3	133 (42 – 353)	0.743
CRP levels, mg/dL	4.1 ± 4.1	2 (0 – 15)	6.1 ± 5.4	7 (1 – 15)	0.564
Fasting Glucose, mg/dL	104.2 ± 36.7	93 (74 – 254)	112.9 ± 23.3	111 (84 – 163)	0.147

Abbreviations; DH: Dermatitis Herpetiformis, IHD: Ischemic Heart Disease, LDL: Low-density lipoprotein, HD: High-density lipoprotein, CRP: C-Reactive Protein, SD: standard deviation. Mann-Whitney U test was used. Significant p values were shown in bold and with double star superscript (**) sign.

1,47) (3). In our study, no investigated feature showed a significant relationship with the presence of ischemic heart disease among DH patients, except that being male and older was associated with higher ischemic disease as expected in the general population. When DH patients were compared among themselves, celiac autoantibody positivity, laboratory values, or treatments received did not show a significant correlation with the presence of ischemic heart disease. Since this study is in retrospective methodology, these results should be considered as the prevalence of heart disease evaluated at any given time in DH patients. The incidence may vary in long-term follow-up studies.

This study revealed that HDL cholesterol levels, which are protective in terms of ischemic heart disease, were significantly lower in the DH patients than controls, and LDL and triglyceride levels were similar between the patients with DH and the control group. Inconsistently, in a study investigating cardiac risk factors in DH patients, patients with DH showed significantly favorable lipid profile including higher HDL and lower cholesterol and triglycerides (5). In this study, compliance to an appropriate gluten-free diet in DH patients was reported as 76% and use of dapsone was reported as 69% in total (5). In our series, a total of 33.3% of the patients were using dapsone, but although a gluten-free diet was recommended for all patients, reliable data could not be obtained regarding the dietary compliance of the patients. In a study conducted on celiac patients, it was observed that a gluten-free diet decreased triglycerides and increased HDL (6). Non-compliance with the recommended diet may be one of the reasons why lipids, which show a risk of ischemic heart disease, were not found to be more favorable in DH patients compared to the control group in our study. However, the fact that the DH patients in the aforementioned study were individuals who were not obese, came from upper social class, and smoked less than the control group may also be the reason for the results such as better lipid profile in the DH group, unlike our study (5). Another possible pathogenesis of lipid profile changes in DH patients has been suggested as atrophy of intestinal villi involved in the synthesis of lipids (5). In our series, the prevalence of celiac disease in DH patients was found to be as high as 72.2%.

The prevalence of DM was significantly higher in DH patients in our study. However, urinary protein, urine glucose, and fasting glucose levels were similar between DH patients and controls; this suggests that the difference in DM prevalence may not be

responsible for the lipid profile differences of DH patients.

In terms of risk factors for future ischemic heart disease, the presence of hypertension was similar between the patients with DH and control group. In a comprehensive registry-based investigation, there were no notable differences in the prevalence of hypertension and hypercholesterolemia between the DH group and the control group (3). Hypertension does not appear to be a significant risk factor that can be linked to DH and cardiac morbidity.

The limitation of this study, as in all retrospective studies, is that the frequency of risk factors can be evaluated according to existing patient records. Prospective controlled studies with long term follow-up are needed to evaluate the true prevalence of ischemic heart disease in these patients.

CONCLUSION

In conclusion, this study revealed that the presence of ischemic heart disease and known cardiovascular risk factors, such as LDL cholesterol, triglyceride, fasting glucose levels and hypertension were similar in DH patients compared to general population. However, HDL cholesterol, which is protective in terms of ischemic heart disease, was significantly lower in the DH patients compared to controls. Considering the increased rates of ischemic heart disease among celiac patients, this result indicates the necessity for additional studies to comprehensively understand the connection between DH and cardiovascular conditions along with the potential underlying mechanisms. Prospective studies with long-term follow-up can help determine the true cardiovascular risk for DH patients and therefore optimize their health in this context.

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