Original Article

Exploring the Potential Link: Atherosclerosis and Chronic Spontaneous Urticaria: Analyzing Lipid-Related Atherosclerosis Markers in 203 Patients at a Specialized Urticaria Outpatient Clinic in a Tertiary Center

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Abstract

Background: This study investigated the relationship between Chronic spontaneous urticaria and atherogenic dyslipidemia. **Methods:** The study retrospectively screened 203 patients diagnosed with CSU and 182 healthy controls between January 2017 and January 2024. We compared the weight of the atherogenic component in the cholesterol components of patients with CSU. The same comparisons were made in patients and control groups when those with total lipid levels below ≤ 200 mg/dL were selected. **Results:** Atherogenicity markers such as Atherogenic index of plasma (AIP) (p<0.001), remnant lipoproteins (p<0.001), non-HDL-C (p=0.031), and non-HDL to HDL-C ratio (p=0.043) values were higher in the CSU group compared to the healthy control group. While this situation was similar in the female gender, statistical significance remained only for AIP (p=0.004) and remnant lipoproteins (p=0.043) among these parameters in males. While there was statistical significance for AIP (p=0.004) and remnant lipoproteins (p=0.043) in patients with total cholesterol levels ≤ 200 mg/dL, no significant differences were detected for the markers non-HDL-C (p=0.545) and non-HDL-C to HDL-C (p=0.292). **Conclusions:** Atherogenic lipids may be markers that may able to differentiate patients with the potential to develop CSU.

Keywords: *AIP, Atherogenic index of plasma, atherogenic dyslipidemia, Chronic spontaneous urticaria, Non-HDL to HDL ratio, Remnant lipoproteins, non-HDL cholesterol*

Introduction

Atherosclerosis is a chronic, age-dependent disease caused by plaques formed by the accumulation of proatherogenic lipids and lipoproteins in the arterial intima, in which both inflammatory and immune mechanisms are responsible. This deposition causes both structural and functional deterioration in endothelial cells of the vessels. Monocytes cross the endothelial barrier to clear these lipids and differentiate into macrophages.[1] While the purpose of macrophages is to clear the accumulated lipid cells, the excess of this accumulation results in their transformation into foam cells. These foam cells enable the development of

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atherosclerotic plaques and aggravate inflammation with the proinflammatory substances they secrete.[1,2]

Low-density lipoprotein cholesterol (LDL-C) has long been regarded as a key player in this scenario, with its elevation identified as a risk factor for atherosclerosis. However, a shift in perspective has emerged in recent years, acknowledging that beyond LDL-C, other lipid fractions also contribute to atherogenicity. These supplementary lipids are termed atherogenic lipids.[2]

Chronic spontaneous urticaria (CSU) is characterized by the simultaneous occurrence and subsequent regression of skin swelling, angioedema, or both, which persist for more than 6 weeks.[3] While the precise cause of CSU remains not fully understood, factors such as autoimmune disorders, histamine-releasing agents, and cellular abnormalities have been implicated.[4] Most studies investigating the relationship between CSU and hyperlipidemia have been conducted within the past decade.[5,6]

Inflammation is the most common hypothesis for the relationship between hyperlipidemia and CSU, although the exact connection is unclear.[7] Mast cells play a significant role in the pathogenesis of hyperlipidemia, CSU, and atherosclerosis. The role of inflammatory mast cells in the development of atherosclerosis and plaque stabilization is now well understood.[8,9] Research on the relationship between mast cells and atherosclerosis dates back to the 1950s.[8] Mast cells are found in both the intima and perivascular tissues of atherosclerotic plaques.[9] Mast cells actively participate in atherosclerosis by releasing proangiogenic VEGF-A, prolympangiogenic VEGF-C, and VEGF-D.[10] In the pathogenesis of chronic urticaria, mast cells' reactivity increases due to local inflammatory cytokines and neuropeptides.[11]

Numerous studies have been designed to investigate whether CSU affects the cardiovascular system or other body systems. However, these studies have yielded conflicting results.[3–6] In the retrospective analysis conducted by Egeberg *et al*.[12] in 2017 with 2215 CSU patients, no increase in cardiovascular system diseases was shown. On the other hand, in the study published in 2024, Andrade *et al*.[13] reported a significant relationship between CSU and cardiovascular events in their study. These were mostly prevalence-related studies. Our study was designed to show that lipids and lipid-related parameters could also shed light on the CSU–atherosclerosis relationship. We set out with the idea that the atherogenic index of plasma could be a suitable parameter for this purpose.

In addition to all these indexes and calculations, the atherogenic index of plasma (AIP), formulated as log (triglyceride/HDL-C), has been gaining popularity in recent years as an indicator of cardiovascular risk.[14] Kardiyovasküler system hastalıklarında[15] artık geçerli bir belirteçken, diğer bazı başka hastalıklar için de araştırılmakta ve ilgi bağı kurulmaktadır.[16]

VLDL (very low-density lipoprotein), VLDL remnants, intermediate-density lipoprotein (IDL), LDL, and lipoprotein [Lp (a)] with diameters of up to approximately 70 nm are capable of passing through the endothelium. While LDL is the lipoprotein that delivers the most cholesterol to the artery wall, it is not the sole contributor.[17,18] In addition, it is known that apolipoprotein CIII containing triglyceride-rich lipoproteins (apoCIII-TGRL), which have rapid turnover features, contributes to the formation of atherogenic LDL fractions.[19]

Triglyceride-rich particles and their remnants, which include cholesterol fragments, have gained prominence in the pathogenesis of atherosclerotic heart diseases. These remnants are primarily formed from intestinally derived chylomicrons and VLDLs originating from the liver. In our article, we will prefer to define these as "remnant lipoproteins".[20] These remnant particles are smaller in size compared to chylomicrons and VLDL, making it easier for them to transcytose into the arterial intima within the plaque region. Here, they adhere through electrostatic interactions between their main polyproteins (apolipoprotein B and apolipoprotein E) and matrix proteoglycans.[18]

An alternative method for assessing the atherogenic risk in patients with CSU involves indirectly calculating atherogenic lipids within the total cholesterol profile. Numerous studies have suggested that non-HDL cholesterol[21] plays a role in atherobiology, and the ratio of non-HDL-C to HDL-C can predict atherosclerosis to a degree comparable to LDL.[22-24]

This study represents the initial comparison of AIP levels between individuals with CSU and healthy controls.

Material and Methods

This study retrospectively screened patients with CSU from January 2017 to January 2024 at the Dermatology Clinic of Kayseri Medical School, Kayseri City Training and Research Hospital, affiliated with Sağlık Bilimleri University. This study was conducted in compliance with the Helsinki Declaration and received approval from the local ethics committee (Approval code: 404/03.06.2021).

The records of 869 patients with CSU, who were followed for chronic urticaria and whose data are kept regularly, were carefully examined, and 203 patients with CSU who met the exclusion criteria were included

in the study. CSU files created for each patient in the hospital's computer database were reviewed. General patient information (Body-mass index, age, comorbidities, smoking status, etc.) and CSU-specific data (such as UAS1, angioedema, and whether the disease was in remission or active) were obtained from this records system. Biochemical data were gathered by examining laboratory records from the hospital database. The reasons why the remaining 666 patients were excluded from the study are shown in Figure 1. Ultimately, 203 patients remained in the study. The control group consisted of 182 consecutive healthy individuals with similar demographic characteristics. The control group was also required to have no history of atopic, autoimmune, or metabolic diseases.

In the initial stage, we compared 203 patients diagnosed with CSU and a matched healthy control group. Following this, patients exhibiting serum total cholesterol levels exceeding 200 mg/dL[25,26] were excluded, and subsequent statistical analyses were performed on the remaining patients and healthy controls. This two-stage analytical approach aimed to investigate potential differences in atherogenic indexes among patients with normal total cholesterol levels.

In the second stage, the cohort consisted of 138 patients diagnosed with CSU alongside 147 healthy controls. Our primary aim was to assess the atherogenic component's impact on serum total cholesterol levels in CSU patients, rather than diagnosing dyslipidemia within this group.

Patients were categorized and compared based on their urticaria activity scores 1 (UAS1), which were self-reported by patients daily to document pruritus severity and wheal count. Data of UAS1 were collected over 7 days and scored, with a maximum total of 6 [Table 1]. UAS is considered the gold standard for activity measurement in CSU. The UAS was specifically developed for use in patients with CSU. It is the recommended method for assessing the activity of CSU and response to the treatment according to the European Academy of Allergy and Clinical Immunology/Global Allergy and Asthma European Network/European Dermatology Forum/World Allergy Organization guideline for urticaria.[27-29]

Calculation of parameters

The lipid parameters recorded for the patients included total cholesterol, LDL-C, HDL-C, and triglyceride values. The non-HDL-C value was derived by subtracting HDL-C from total cholesterol.[21] To obtain the non-HDL-C to HDL-C ratio, the non-HDL-C value was divided by the HDL-C value. Additionally, the AIP was calculated by taking the logarithm of the ratio of triglycerides to HDL-C (log triglyceride/HDL-C).[30] Triglyceride and HDL-C units in mg/dL were converted into mmol/L for these calculations.

Statistical analyses

The data distribution characteristics were examined using histograms and the Shapiro–Wilk test. While continuous variables conforming to normal distribution were presented as mean ± standard deviation, those that did not meet the normal distribution criteria were expressed as median (minimum–maximum). The Mann–Whitney U test was used to compare continuous variables of independent groups that did not conform to normal distribution. Those that conformed to normal distribution were compared with Student's T-test. Categorical variables were compared using the Chi-square test or Fisher's exact test. Pearson correlation analysis or Spearman's correlation analysis was employed to determine the relationships between variables as suitable. Receiver operating characteristic (ROC) curves were constructed to evaluate the lipid-related variables' performance in indicating the presence of CSU. Univariate binary logistic regression analysis was conducted to assess potential risk factors for CSU development. A significance level of $P < 0.050$ was applied. All statistical analyses were performed using the Statistical Package Program for Social Sciences, version 23.0 (IBM Corporation, Armonk, NY, USA).

Results

Demographic characteristics

In this study, the data from 203 patients diagnosed with CSU were compared to those of 182 healthy individuals in the control group. In the study group, the mean age was 34.6 ± 10.4 years, and in the control group, it was 36.3 ± 11.9 years ($P = 0.133$). Moreover, both groups exhibited similar gender distributions. In the study group, the male/female ratio was 25.1%/74.9% (n = 51/152), and in the control group, it was 28.0%/72.0% (n = 51/131) ($P = 0.520$).

Urticaria activity score (UAS)

No statistically significant correlations were identified between the UAS1 scores of patients with CSU and their body mass index, serum lipid levels, serum IgE levels, age at onset of the disease, or disease duration, AIP,

Table 1: Urticaria activation score 1 (UAS1)

Score	Wheal	Pruritus
0	None	None
1	Mild: <20 in 24 h	Mild: Exists but not disturbing
2	Moderate: 20–50 in 24 h	Moderate: Disturbing but not disrupting sleep or daily activity
3	Severe	Severe: Disrupts sleep and daily activity

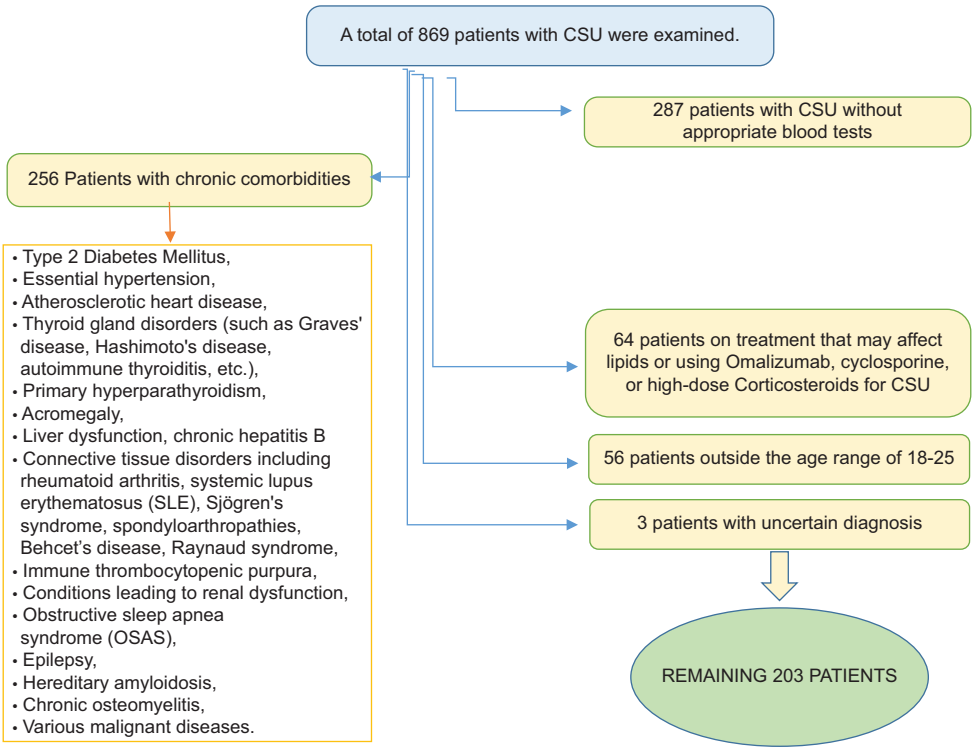

Figure 1: Exclusion diagram of patients with CSU followed by the authors of our group in the chronic urticaria outpatient clinic. In total, the records of 869 patients were reviewed; after applying the exclusion criteria, 203 patients remained, who could be used in the study

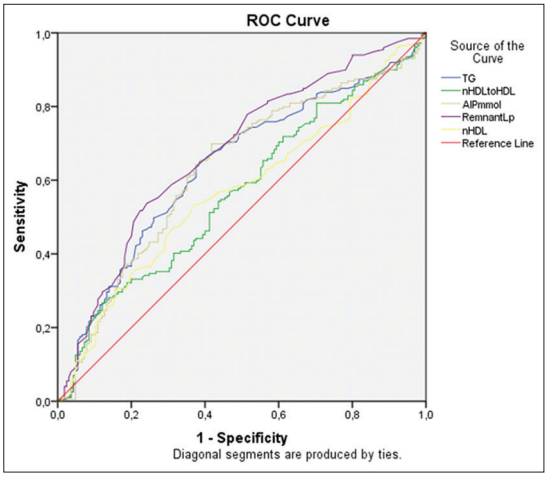

Figure 2: ROC curve for parameters predictive of CSU

remnant lipoproteins, Non-HDL-C, or the Non-HDL-C to HDL-C ratio [Table 2].

Lipid profiles

A comparison between patients with CSU and healthy controls regarding serum lipids and lipid-related atherosclerotic parameters is presented in Table 3. Serum HDL-C, triglyceride, AIP, non-HDL-C, non-HDL to HDL-C ratio, and remnant lipoproteins were found to be significantly higher in the CSU than in healthy controls:

- The serum triglyceride value was median 118 (29–419) mg/dL in healthy controls, while median 144.8 (41-433) mg/dL in CSU patients ($P < 0.001$).
- Serum AIP was median 0.04 (-0.74–0.55) in control group patients, while median 0.05 (-0.54-0.80) in CSU patients ($P < 0.001$).
- Remnant lipoproteins were median 23 (5-54) mg/dL in healthy controls, while median 25 (0-63) mg/dL in CSU patients ($P < 0.001$).
- Non-HDL-C was 2.58 ± 1.062.58 ± 1.06 mg/dL in healthy controls. In patients with CSU, it was 2.81 ± 1.14 mg/dL ($P < 0.031$).
- Non-HDL/HDL-C was 2.58 ± 1.06 mg/dL in healthy controls and 2.81 ± 1.14 mg/dL in those with CSU ($P < 0.043$).

There were weak, positive, and statistically significant correlations between the age of CSU onset and non-HDL-C (r = 0.416, $P < 0.001$), non-HDL-C to HDL-C ratio (r = 0.256, $P = 0.003$), AIP (r = 0.243, $P = 0.004$), and remnant lipoproteins (r = 0.268, $P = 0.002$).

The correlations between CSU duration and lipid parameters were not statistically significant.

ROC analyses and AUC values are used to compare the power of lipid parameters to predict CSU. LDL-c, HDL-c, and age were not found to be statistically significant in terms of predicting the presence of CSU (P values > 0.005 for each parameter). Total cholesterol, triglyceride, non-HDL-C, non-HDL-C

Table 2: The percentage of body areas affected by pemphigus vulgaris and bullous pemphigoid

	Pemphigus Vulgaris (*n*=35)				Bullous Pemphigoid (*n*=33)			
	Involvement Rates of PV	Relapse (-)	Relapse (+)	*P*1	Involvement Rates of BP	Relapse (-)	Relapse (+)	*P*2
Oral mucosal involvement	91.4% (*n*=32)	94.4% (*n*=17/18)	88.2% (*n*=15/17)	0.603	24.2% (*n*=8)	25.9% (*n*=7/27)	16.7% (*n*=1/6)	
Total gingival involvement	40.0% (*n*=14)	50.0% (*n*=9/18)	29.4% (*n*=5/17)	0.214	9.1% (*n*=3)	11.1% (*n*=3/27)	0% (*n*=0/6)	
Upper gingival mucosal involvement	31.4% (*n*=11)	38.9% (*n*=7/18)	23.5% (*n*=4/17)	0.328	6.1% (*n*=2)	7.4% (*n*=2/27)	0% (*n*=0/6)	
Lower gingival mucosal involvement	31.4% (*n*=11)	50.0% (*n*=9/18)	11.8% (*n*=2/17)	0.015	3.0% (*n*=1)	3.7% (*n*=1/27)	0% (*n*=0/6)	
Lower lip involvement	31.4% (*n*=11)	44.4% (*n*=8/18)	17.6% (*n*=3/17)	0.088	9.1% (*n*=3)	11.1% (*n*=3/27)	0% (*n*=0/6)	
Total buccal mucosa involvement	74.3% (*n*=26)	72.2% (*n*=13/18)	76.5% (*n*=13/17)	1.000	12.1% (*n*=4)	11.1% (*n*=3/27)	16.7% (*n*=1/6)	
Left buccal mucosa involvement	62.9% (*n*=22)	61.1% (*n*=11/18)	64.7% (*n*=11/17)	0.826	12.1% (*n*=4)	11.1% (*n*=3/27)	16.7% (*n*=1/6)	
Right buccal mucosa involvement	65.7% (*n*=23)	66.7% (*n*=12/18)	64.7% (*n*=11/17)	0.903	9.1% (*n*=3)	11.1% (*n*=3/27)	0% (*n*=0/6)	
Total palate mucosal involvement	37.1% (*n*=13)	50.0% (*n*=9/18)	23.5% (*n*=4/17)	0.105	6.1% (*n*=2)	7.4% (*n*=2/27)	0% (*n*=0/6)	
Hard palate mucosal involvement	28.6% (*n*=10)	38.9% (*n*=7/18)	17.6% (*n*=3/17)	0.164	3.0% (*n*=1)	3.7% (*n*=1/27)	0% (*n*=0/6)	
Soft palate mucosal involvement	20.0% (*n*=7)	22.2% (*n*=4/18)	17.6% (*n*=3/17)	1.000	3.0% (*n*=1)	3.7% (*n*=1/27)	0% (*n*=0/6)	
Floor-of-mouth mucosal involvement	17.1% (*n*=6)	22.2% (*n*=4/18)	11.8% (*n*=2/17)	0.658	No involvement	No involvement	No involvement	
Tongue involvement	40.0% (*n*=14)	55.6% (*n*=10/18)	23.5% (*n*=4/17)	0.053	3.0% (*n*=1)	3.7% (*n*=1/27)	0% (*n*=0/6)	
Pharyngeal involvement	11.4% (*n*=4)	5.6% (*n*=1/18)	17.6% (*n*=3/17)	0.338	No involvement	No involvement	No involvement	*P*>0.050
Esophageal involvement	No involvement	No involvement	No involvement		6.1% (*n*=2)	7.4% (*n*=2/27)	0% (*n*=0/6)	
Truncal involvement	28.6% (*n*=10)	27.8% (*n*=5/18)	29.4% (*n*=5/17)	0.915	72.7% (*n*=24)	66.7% (*n*=9/27)	100% (*n*=6/6)	
Extremity involvement	22.9% (*n*=8)	33.3% (*n*=6/18)	11.8% (*n*=2/17)	0.228	87.9% (*n*=29)	88.9% (*n*=24/27)	83.3% (*n*=5/6)	
Head and neck region involvement	25.7% (*n*=9)	16.7% (*n*=3/18)	35.3% (*n*=6/17)	0.264	33.3% (*n*=11)	25.9% (*n*=7/27)	66.7% (*n*=4/6)	

Table 3: There are three separate comparisons in the table. The first includes comparing patients with CSU and the healthy control group, the second includes comparing only male patients with CSU and healthy controls, and the third includes comparing only female CSU patients with healthy controls in terms of lipid and lipid-related parameters

Variables	Healthy controls (*n*=182)	CSU (*n*=203)	*P*	Healthy men (*n*=51)	CSU men (*n*=51)	*P*	Healthy women (*n*=131)	CSU women (*n*=152)	*P*
Age (years)	34.6±10.4	36.3±11.9	0.133	37.8±11.3	38.5±11.3	0.796	33.4±9.8	35.6±11.9	0.073
BMI (kg/m^2)									
Total Cholesterol (mg/dL)	175.2±33.2	181.6±33.8	0.063	178.4±36.8	181.3±37.8	0.695	174.0±31.8	181.7±32.5	0.045
LDL-c (mg/dL)	104.3±30.0	104.1±29.5	0.942	108.7±33.8	107.5±32.6	0.856	102.6±28.4	107.5±32.6	0.916
HDL-c (mg/dL)	51.5±12.4	50.4±13.1	0.426	44.6±11.1	44.4±10.3	0.934	54.2±11.9	52.5±13.5	0.264
Triglyceride (mg/dL)	118 (29-419)	144.8 (41-433)	<0.001	112 (50-686)	165 (44-525)	0.023	90 (31-462)	124.5 (33-185)	<0.001
Remnant lipoproteins (mg/dL)	23 (5-54)	25 (0-63)	<0.001	18.5 (0-165.0)	29.0 (1.0-60.0)	0.004	15 (0-79)	22 (0-91)	<0.001
AIP	0.04 (-0.74-0.55)	0.05 (-0.54-0.80)	<0.001	0.05 (-0.42-0.99)	0.18 (-0.62-0.83)	0.043	-0.13 (-0.66-0.85)	0.04 (-0.74-0.60)	<0.001
Non-HDL-c	123.7±32.7	131.2±34.3	0.031	133.8±35.4	136.8±36.6	0.667	133.8±35.4	136.8±36.6	0.015
Non-HDL/HDL-c	2.58±1.06	2.81±1.14	0.043	3.19±1.26	3.22±1.07	0.897	3.19±1.26	3.22±1.07	0.006

Table 4: ROC analysis and area under the curves (AUC) were employed to evaluate the predictive performance of lipid parameters for CSU patients

Variables	AUC	95% CI	*P*
Remnant lipoproteins	0.676	0.502-0.688	<0.001
Triglycerides	0.636	0.579-0.694	<0.001
Atherogenic Index of Plasma (AIP)	0.630	0.620-0.731	<0.001
Non-HDL-C	0.568	0.509-0.627	0.025
Non-HDL/HDL	0.566	0.507-0.624	0.031
Total Cholesterol	0.565	0.506-0.624	0.031

to HDL-C ratio, AIP, and remnant lipoproteins were capable of predicting the presence of CSU at a moderate level. These results were found to be statistically significant. Parameters with the significant area under curves are shown in Table 4 and Figure 2.

Table 5 displays the odds ratios indicating the extent to which lipid parameters may serve as risk factors for CSU. Univariate binary logistic regression analyses were conducted to assess the impact of lipid parameters on CSU. Remnant lipoproteins, AIP, non-HDL-C, and the non-HDL-C to HDL-C ratio were identified as independent risk factors for CSU.

Gender

When comparing lipid parameters of the control group and CSU group exclusively among males, most comparisons were found to be statistically insignificant, except for LDL-C, which was higher in the control group [Table 3].

The most notable distinctions emerged in the analysis of lipid parameters among females. Within the CSU group, serum triglycerides, total cholesterol, AIP, remnant lipoproteins, non-HDL-C, and the non-HDL-C to HDL-C ratio exhibited significant elevations.

Atopic comorbidities

When the patients were divided into two groups based on the presence or absence of atopic comorbidities, statistically significant differences were not observed in terms of lipids or lipid-related atherosclerotic parameters [Table 6].

Angioedema

When patients with CSU were grouped into those with and without angioedema, statistically significant differences were observed in lipid-related parameters. Specifically, serum triglyceride and LDL-C levels were significantly lower, while HDL-C levels were significantly higher in patients with angioedema. Additionally, the AIP, non-HDL-C, and non-HDL-C to HDL-C ratios were lower in patients with angioedema compared to those without [Table 6].

Table 5: Odds ratios indicating the likelihood of age and lipid levels as risk factors for CSU, along with their 95% confidence intervals, derived from binary logistic regression analysis, are presented below

VARİABLES	Odds ratio	95% CI	*P*
Remnant lipoproteins	1.029	1.014-1.045	<0.001
Atherogenic Index of Plasma (AIP)	3.584	1.725-7.448	0.001
Triglycerides	1.005	1.002-1.008	0.001
Non-HDL-c	1.007	1.001-1.013	0.032
Non-HDL-c to HDL-c	1.214	1.004-1.467	0.045
Total Cholesterol	1.006	1.000-1.012	0.064
Age	1.014	0.996-1.032	0.136
HDL-c	0.994	0.978-1.009	0.426
Gender	0.862	0.548-1.356	0.520
LDL-c	1.000	0.993-1.007	0.942

Omalizumab necessity

Lipid values obtained from patients with CSU undergoing treatment with omalizumab, cyclosporine, or high-dose corticosteroids were excluded from the analysis . However, values obtained before the treatments commenced were used for some patients. These patients were divided into two groups: those who required omalizumab and those who did not. Lipid values and lipid parameters of patients requiring omalizumab were found to be lower than those of the other group, and this difference was statistically significant [Table 6].

Body mass indexes (BMI)

Regarding BMI, no association was found between the obese group (BMI ≥30) and others (BMI <30) in terms of disease activity (P = 0.257), atopic comorbidities (P = 0.335), presence of angioedema (P = 0.426), initiation of Omalizumab treatment (P = 0.187), or symptomatic dermographism (P = 0.257).

In patients with CSU, there exists a positive but weak statistical correlation between BMI and total cholesterol (r = 0.206, P = 0.032), LDL-c (r = 0.211, P = 0.029), triglycerides (r = 0.250, P = 0.009), non-HDL-c (r = 0.265, P = 0.005), non-HDL to HDL ratio (r = 0.267, P = 0.005), AIPs (r = 0.281, P = 0.003), and remnant lipoproteins (r = 0.229, P = 0.018).

IgE Levels and other parameters

In patients with CSU, there is a positive but weak statistical correlation between serum IgE levels and total cholesterol (r = 0.218, P = 0.021), LDL-c (r = 0.234, P = 0.013), and non-HDL-C (r = 0.205, P = 0.030). However, there is a negative but weak statistical correlation between serum IgE levels and HDL-C levels (r = -0.198, P = 0.039).

There is no statistical significance in the correlations between serum IgE levels and triglyceride, non-HDL to HDL ratio, AIP, remnant lipoproteins, and BMI of patients with CSU.

In a similar vein, Table 3 outlines the comparisons of smokers, patients in remission, those displaying symptomatic dermographism, and individuals with hot urticaria with other CSU patients within the group [Table 6].

Comparisons of two groups among cases with total cholesterol level < 200 mg/dL

In the second stage of the analysis, only individuals with total cholesterol levels below 200 mg/dL were included to better evaluate the association between lipids and lipid-related parameters with CSU; cases above this value were not included in the analyses.

In this scenario, LDL-C, triglycerides, AIP, and remnant lipoproteins remained significantly elevated in the CSU group with high statistical significance. Relevant calculations are summarized in Table 7.

When examining solely male participants within the identical cohort, remnant lipoproteins emerged as the sole parameter exhibiting a notable elevation [Table 7].

Similarly, among female patients with total cholesterol levels ≤ 200 mg/dL, triglycerides, AIP, and remnant lipoproteins were found to be significantly higher in the CSU group [Table 7].

Discussion

In this study, we focused on hyperlipidemia, a well-known risk factor for atherosclerosis, within the context of CSU. The primary aim of this study was to elucidate more clearly the significance of lipids in CSU. Parameters such as the AIP, non-HDL-C, and the non-HDL-C to HDL-C ratio, which have emerged as crucial indicators of atherosclerosis today, were also collectively examined in this study. Additionally, remnant lipoproteins, now recognized as major contributors to atherosclerosis, were also addressed within the scope of this investigation.

Various predisposing conditions can contribute to the development of atherosclerosis and cardiovascular diseases. Additionally, the stress and mediators induced by these conditions may also play a significant role.[31] The INTER-HEART study demonstrated that the presence of chronic stress significantly elevates the risk of acute coronary syndrome.[32] In this context, CSU has been investigated in various ways regarding its potential contribution to atherosclerosis.[33,34]

Table 6: Patients with CSU were grouped according to gender, atopic disease, angioedema, need for omalizumab or not, smoking status, presence or absence of hot urticaria, whether CSU was in remission or active phase, and whether symptomatic dermographism was present. According to these created groups, they were compared in terms of lipids and lipid-related parameters and summarized as a single table

Variables	Male (*n*=51)	Female (*n*=152)	*P*	CSU without Atopic comorbidity (*n*=72)	CSU with Atopic comorbidity (*n*=62)	*P*
Age (years)	38.5±14.5	35.6±10.9	0.202	34.3±11.9	35.3±11.7	0.622
BMI (kg/m^2)	26.3±3.1	26.3±5.5	0.999	25.5±4.3	27.2±5.5	0.073
Total Cholesterol (mg/dL)	181.3±37.8	181.7±32.5	0.931	177.5±32.8	182.2±34.0	0.424
LDL-c (mg/dL)	107.5±32.6	102.9±28.4	0.347	100.4±29.8	103.9±29.2	0.496
HDL-c (mg/dL)	44.4±10.3	52.5±13.4	<0.001	51.1±13.2	52.0±15.0	0.710
Triglyceride (mg/dL)	165 (44-525)	124.5 (29-419)	0.010	118 (29-419)	144.8 (41-433)	0.491
Remnant lipoproteins (mg/dL)	29 (1-60)	22 (0-91)	0.050	23 (5-54)	25 (0-63)	0.603
AIP	0.22 (-0.62-0.83)	0.04 (-0.74-0.60)	0.001	0.04 (-0.74-0.55)	0.05 (-0.54-0.80)	0.908
Non-HDL-c	136.8±36.6	129.3±33.3	0.174	126.4±34.2	130.1±34.2	0.530
Non-HDL/HDL-c	3.22±1.07	2.67±1.14	0.002	2.70±1.31	2.72±1.09	0.959
IgE	106.7 (7.8-883.0)	132.0 (4.0-2071.0)	0.930	113.7 (4.0-758.8)	128.1 (17-1654)	0.811
Variables	**Non-Smokers (*n*=102)**	**Smokers (*n*=34)**	***P***	**Hot Urticaria absent (*n*=18)**	**Hot Urticaria present (*n*=20)**	***P***
Age (years)	34.8±11.6	34.8±12.5	0.987	30.1±10.6	36.0±10.6	0.060
BMI (kg/m^2)	26.5±5.2	25.6±4.1	0.388	26.0±5.7	26.1±4.4	0.992
Total Cholesterol (mg/dL)	180.6±35.1	175.1±26.8	0.385	181.3±37.8	181.7±32.5	0.946
LDL-c (mg/dL)	102.7±31.3	100.2±22.0	0.620	111.1±36.4	102.5±25.9	0.357
HDL-c (mg/dL)	52.4±14.0	48.4±13.6	0.143	47.3±10.8	51.9±12.3	0.207
Triglyceride (mg/dL)	183 (30-525)	139.5 (29-433)	0.644	140.5 (41-433)	129.5 (54-301)	0.973
Remnant lipoproteins (mg/dL)	23 (0-63)	25 (6-60)	0.658	25 (8-49)	25 (11-60)	0.335
AIP	0.03 (-0.60-0.55)	0.11 (-0.74-0.80)	0.411	0.07 (-0.54-0.80)	0.03 (-0.40-0.60)	0.770
Non-HDL-c	128.4±35.5	126.8±28.9	0.806	135.6±43.1	131.4±30.3	0.729
Non-HDL/HDL-c	2.67±1.25	2.86±1.06	0.426	3.0±1.14	2.81±1.58	0.651
Variables	**CSU without Angioedema (*n*=69)**	**CSU with Angioedema (*n*=67)**	***P***	**CSU (*n*=115)**	**CSU required Omalizumab (*n*=18)**	***P***
Age (years)	34.3±11.9	33.8±13.5	0.318	35.0±11.7	32.8±12.1	0.458
BMI (kg/m^2)	26.3±4.5	26.3±5.6	0.960	26.5±5.0	25.1±4.5	0.279
Total Cholesterol (mg/dL)	182.7±34.0	176.0±33.4	0.243	180.1±33.3	172.3±32.0	0.354
LDL-c (mg/dL)	106.8±30.0	97.2±28.3	0.059	103.7±30.2	89.5±20.7	0.017
HDL-c (mg/dL)	48.1±12.2	54.8±14.9	0.005	50.0±13.3	59.6±15.1	0.006
Triglyceride (mg/dL)	144 (40-433)	112 (29-317)	0.009	128 (29-433)	95 (31-242)	0.057
Remnant lipoproteins (mg/dL)	27 (0-60)	23 (5-63)	0.032	24.0 (0-63.0)	18,0 (6.2-48.0)	0.237
AIP	0.13 (-0.56-0.80)	-0.03 (-0.74-0.50)	0.001	0.05 (-0.74-0.80)	-0.17 (-0.62-0.29)	0.009
Non-HDL-c	134.5±33.0	121.3±33.7	0.022	130.1±34.4	112.7±28.1	0.044
Non-HDL/HDL-c	2.75±1.31	2.40±0.99	0.002	2.83±1.24	1.24±0.64	<0.001
IgE	124 (17-1654)	123.7 (4.0-736.7)	0.674	124 (17-1654)	123.7 (4.0-736.7)	0.279
Variables	**Remission (*n*=37)**	**Active disease (*n*=101)**	***P***	**Symptomatic Dermographism absent (*n*=26)**	**Symptomatic Dermographism present (*n*=20)**	***P***
Age (years)	37.9±11.8	33.9±11.7	0.082	34.6±10.4	37.7±11.4	0.343
BMI (kg/m^2)	26.5±5.6	26.3±4.8	0.798	25.6±4.1	28.1±4.0	0.056
Total Cholesterol (mg/dL)	184.0±34.8	178.0±32.2	0.341	182.1±38.3	182.0±27.5	0.990
LDL-c (mg/dL)	111.1±28.2	99.1±28.9	0.032	103.2±33.0	106.3±25.6	0.734
HDL-c (mg/dL)	49.6±52.0	52.0±14.4	0.356	47.3±10.8	51.9±12.3	0.495
Triglyceride (mg/dL)	128 (40-433)	127 (29-419)	0.648	133.0 (41.0-301.0)	125.5 (31.0-260.0)	0.650
Remnant lipoproteins (mg/dL)	21 (0-63)	25 (5-60)	0.168	25.0 (8.0-49.0)	26.0 (6.2-45.0)	0.864
AIP	0.05 (-0.67-0.99)	0.05 (-0.75-0.60)	0.504	0.04 (-0.45-0.60)	0.15 (-0.62-0.41)	0.674
Non-HDL-c	134.4±36.1	125.9±32.6	0.190	130.1±38.80	132.9±32.0	0.797
Non-HDL/HDL-c	2.99±1.56	2.62±1.03	0.111	2.67±1.13	3.17±1.86	0.268

Table 7: This table includes comparisons of patients with CSU and healthy controls, with total cholesterol levels below ≤200 mg/dL in both groups. There are three separate comparisons in the table. The first includes comparing patients with CSU and the healthy control group, the second includes comparing only male patients with CSU and healthy controls, and the third includes comparing only female CSU patients with healthy controls regarding lipid and lipid-related parameters

Variables	Healthy (*n*=147)	CSU (*n*=138)	*P*	Healthy men (*n*=38)	CSU men (*n*=35)	*P*	Healthy women (*n*=109)	CSU women (*n*=103)	*P*
Age (years)	33.6±10.3	33.5±11.4	0.933	36.1±11.7	35.4±14.2	0.857	32.7±9.7	32.8±10.3	0.948
Total Cholesterol (mg/dL)	163.2±21.7	163.4±23.1	0.927	162.2±24.0	159.9±23.1	0.682	163.5±21.0	164.6±23.1	0.720
LDL-c (mg/dL)	95.3±33.8	90.0±32.6	0.032	98.4±20.3	91.2±23.1	0.165	94.2±20.9	89.5±20.5	0.102
HDL-c (mg/dL)	50.8±12.2	49.4±12.1	0.323	44.0±10.6	42.9±10.1	0.681	53.3±11.8	51.6±12.0	0.320
Triglyceride (mg/dL)	15 (31-369)	111 (26-433)	0.007	107 (50-312)	127 (44-433)	0.159	87 (31-369)	104 (29-272)	0.013
Remnant lipoproteins (mg/dL)	15 (0-62)	21 (0-91)	<0.001	17.5 (4.0-62.0)	25.0 (1.0-54.0)	0.019	14 (0-55)	20 (0-91)	<0.001
AIP	-0.12 (-0.66-0.85)	0.01 (-0.74-0.80)	0.008	0.04 (-0.42-0.67)	0.19 (-0.62-0.80)	0.154	-0.17 (-0.66-0.85)	-0.01 (-0.74-0.60)	0.016
Non-HDL-C (mg/dL)	112.3±22.1	114.1±24.3	0.545	118.2±22.0	116.9±23.6	0.813	110.3±21.9	113.0±24.6	0.396
Non-HDL-C/HDL-c (ratio)	2.37±0.88	2.47±0.90	0.292	2.84±0.27	2.87±0.88	0.881	2.21±0.80	2.35±0.87	0.219

Previous studies with designs similar to ours aimed to elucidate the relationships between lipid fractions, total cholesterol, and CSU.[5,6,35] In a retrospective study conducted by Chung *et al.*,[35] it was found that patients diagnosed with CSU were more likely to have a history of hyperlipidemia as observed in our research. Their study had a larger sample size, and the authors acknowledged limitations as they did not directly assess the patients, and the records were not generated by their team. However, almost all of our patients were followed by our author team. The outpatient clinic at the hospital specializing in urticaria was established in 2017 by four of the authors of this research. Most of the cases have been managed by these doctors. Therefore, eliminating factors that could affect the outcome became more feasible in our study.

In our study, we observed consistent results with our hypothesis among patient and control groups with similar total cholesterol levels (in this study <200 mg/dL). Since this particular design has not been previously explored in the context of CSU, citing relevant literature becomes challenging.

Triglycerides

The research revealed significantly elevated serum triglyceride levels in patients with CSU, suggesting its potential role as a predictive factor for CSU. This finding underscores the importance of monitoring triglyceride levels as they could indicate a risk factor for CSU development. In this context, we contend that prevalence studies with substantial patient cohorts[26] may face challenges in adequately discerning comorbidities and other influencing factors like medication usage.[35] While single-center studies with smaller sample sizes[34,36] are often deemed more advantageous for this purpose, their results may be prone to contradiction due to the limited number of samples. Triglyceride levels were identified as an independent risk factor and predictor for CSU.

Non-HDL-C and non-HDL-C to HDL-C ratio

In this study, non-HDL-C and the non-HDL-C to HDL-C ratio were also evaluated as indirect indicators of atherogenic tendencies in CSU patients.[37] Recent data suggest that non-HDL-C is a superior predictor of atherosclerotic cardiovascular diseases compared to LDL-C, highlighting the importance of investigating non-HDL-C in other related conditions.[23,38] In our study, when considering the entire group, non-HDL-C levels were significantly higher in the CSU group, consistent with findings from previous literature.[6,39] These differences were even more pronounced in female patients.

While compiling this article, we did not encounter any studies investigating the non-HDL-C to HDL-C

ratio, a novel marker predictive of atherosclerosis, in patients with CSU. However, in our study, we found that the non-HDL-C to HDL-C ratio was significantly higher in patients with CSU, as was non-HDL-C itself. Both parameters were also moderately predictive of the presence of CSU in ROC analyses. Additionally, both were identified as statistically significant independent risk factors for CSU in logistic regression analyses. Interestingly, this significant association was observed only in the female gender subgroup. However, when considering patients with serum total cholesterol levels below 200 mg/dL, both parameters lost their significance in distinguishing between the CSU and control groups.

Remnant lipoproteins

It is now recognized that the lipid fractions contributing to atherosclerosis extend beyond LDL-C or triglycerides. Chylomicron and VLDL remnants, referred to as remnant lipids, are increasingly acknowledged as pivotal in atherosclerosis, alongside LDL and triglycerides, which traditionally serve as treatment targets. Studies indicate that Apoprotein B48-containing VLDLs accumulate in individuals with elevated serum triglycerides.[40] Remnant lipoproteins, rich in triglycerides, are typically associated with serum triglyceride levels. They can be quantified directly or calculated by subtracting HDL-C and LDL-C from total cholesterol, both methods correlating with atherosclerotic outcomes.[41] We chose the calculation method due to the retrospective nature of the study. Whether calculated for the entire group, as previously stated,[6] or specifically for patients with total cholesterol levels below 200 mg/dL, remnant lipoproteins were observed to be higher in patients with CSU compared to the control group. A larger number of both CSUs and healthy controls were included in our study. The ROC analyses have demonstrated the capacity of remnant lipids to predict the presence of CSU. However, the implications of this information for clinical practice are beyond the scope of our study. Remnant lipoproteins were found to be at significantly higher levels in the CSU group than healthy controls. This trend persisted when analyzing patient and control groups with serum total cholesterol below 200 mg/dL. The gender-based analysis also showed continued statistical significance in both genders. Our study revealed that remnant lipids are moderately predictive of CSU and also serve as an independent risk factor.

Atherogenic Index of Plasma (AIP)

AIP is a metric employed to gauge the risk of atherosclerosis in the body. AIP is calculated as the logarithm of the ratio of triglycerides to HDL-C.[30] In our literature searches, we could not find any publications investigating the relationship between AIP and CSU. Our study aimed to fill this gap and found that AIP was significantly higher in favor of CSU patients. This suggests that attention should be paid to the lipids of patients diagnosed with CSU, as supported by existing literature.[6] AIP was found to be significantly elevated in patients with CSU compared to healthy controls in both the entire group and the subgroup of patients with total cholesterol below 200 mg/dL. It serves as a predictive marker for CSU and has emerged as an independent risk factor for the condition. In both genders, AIP levels were higher in the CSU group compared to healthy controls, with statistically significant differences even after the gender-based division of the groups.

This parameter is widely acknowledged as a robust indicator for atherosclerosis.[14] The notable elevation favoring the CSU group across almost all comparisons is a significant finding worthy of attention. While this study lacks sufficient data and design to suggest investigating every patient with elevated AIP for atherosclerosis, this question warrants exploration through new research designs.

To routinely integrate this relationship into clinical practice, additional studies and the accumulation of data from these studies are necessary. Notably, the association between AIP and CSU demonstrated in our study shows significant potential as a practical tool in clinical settings. It is also essential to highlight that all patients included had no comorbidities and were not on medications that could affect serum lipid levels, allowing for a clearer evaluation of the AIP–CSU relationship. Prospective studies should examine the extent to which CSU patients with elevated AIP levels progress to cardiovascular outcomes and whether the time to these outcomes correlates with AIP levels.

Gender influence

AIP, the non-HDL-C to HDL-C ratio, was significantly higher in men with CSU compared to women. The increase in remnant lipoproteins remained borderline significant at $P = 0.050$, which was the defined threshold for statistical significance. HDL was notably lower in men. Consequently, CSU patients were stratified by gender, and the analyses were reiterated.

Upon examining only men, triglycerides, remnant lipoproteins, and AIP were found to be elevated compared to the control group. In women, these three parameters exhibited greater statistical significance than in men. Moreover, non-HDL-C and the non-HDL-C to HDL-C ratios were notably higher in the CSU group among women. If these markers are to be utilized for predicting clinical atherosclerosis in patients with CSU, attention to the gender factor is imperative. There

are studies in the literature that lipid levels in some diseases are related to gender. For example, one study reported that the relationship between serum lipids and cognitive impairment was more pronounced in older men.[42,43] In another, men had a lower risk of developing hyperlipidemia in hypothyroid patients.[44] The reason for the gender-based difference observed in CSU patients in our study remains unclear. This discrepancy may be related to the impact of sex hormones on lipid levels[45]; however, further research is warranted to clarify this association.

Angioedema

Among the study's findings, it was observed that serum triglyceride and LDL-C levels were significantly lower in patients with a history of angioedema, while HDL-C levels were significantly higher. It is challenging to find strong connections in the literature to explain this relationship. It is known that fatty acids contribute to the pathogenesis of angioedema, but the extent of this contribution is not clear.[46] It is possible to find publications indicating that the composition and distribution of HDL changes in allergic and skin diseases.[47,48] New and more focused designs are needed to elucidate the relationship between lipids and angioedema and its possible causes.

Conclusion

Our study has concluded that lipid-related predictors of atherosclerosis could serve as valuable tools for assessing the risk of atherosclerosis in CSU patients. These indices are cost-effective and easily applicable to patients with CSU. However, while these findings are promising, they require validation and standardization through additional studies before they can be clinically implemented. This research revealed elevated lipid-related atherosclerotic indices in favor of CSU. Despite the reliability of these parameters, particularly AIP, as indicators in existing literature, the design of our study does not suffice to recommend routine further evaluation for atherosclerosis in CSU patients with elevated lipid-related atherosclerosis parameters. Thus, we conclude that dedicated study designs for this purpose are warranted.

Limitations

1. Since the study was retrospective, some patients were excluded from the analysis due to missing data in the records.
2. Lipid values could not be reached in a significant number of patients, and only 1/4 of the patients screened could be used in the study.
3. The strictness of the exclusion criteria had an impact on the numerical amount of patient and control groups that could be used.

Authors' contribution

1. **Associate Professor Dr. Deniz AVCI**, The main conductor of the study. One of the authors who created the text of the article.
2. **Associate Professor Dr. Atıl AVCI,** He is one of the dermatologists working in the chronic urticaria outpatient clinic and worked both in collecting and analyzing the data and contributed to the urticaria part of the article.
3. **Associate Professor Ragıp ERTAŞ**, one of the dermatologists working in the chronic urticaria outpatient clinic, contributed to the collection and analysis of data and played a significant role in the section of the article about urticaria.
4. **Dr. Yılmaz ULAŞ**, a dermatologist at the chronic urticaria outpatient clinic, participated in both data collection and analysis and contributed significantly to the urticaria section of the article.
5. **Professor Dr. Kemal ÖZYURT**, one of the dermatologists working in the chronic urticaria outpatient clinic worked both in collecting and analyzing the data and contributed to the urticaria part of the article.
6. **Associate Professor Ali ÇETİNKAYA,** Took part in both data collection and supervision and the writing part of the atherosclerosis wing of the study.
7. **Professor Dr. Mustafa ATASOY,** one of the dermatologists working in the chronic urticaria outpatient clinic worked both in collecting and analyzing the data and contributed to the urticaria part of the article.

All authors read and approved the final version of the manuscript.

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Conflicts of interest

There are no conflicts of interest.

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