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Journal of Skin and Sexually Transmitted Diseases

Original Article

Serum lipid levels in chronic spontaneous urticaria – An analytical cross-sectional study from a tertiary care center

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Received: 23 June 2022
Accepted: 28 August 2022
EPub Ahead of Print: 02 November 2022
Published: 10 July 2023

DOI
10.25259/JSSTD_32_2022

Quick Response Code:

ABSTRACT

Objectives: The primary objective was to compare serum lipid levels in patients with chronic spontaneous urticaria (CSU) and normal subjects. The secondary objective was to study the clinical profile of patients with CSU.

Materials and Methods: This was a hospital-based analytical cross-sectional study comparing the serum lipid levels in 45 patients with CSU with that of age- and gender-matched normal subjects who attended a tertiary care center during a period of 1 year (January 2020 to December 2020). A structured questionnaire was used to record history and examination findings. Lipid levels were estimated by collecting blood samples after 12 hours of fasting. The data were analyzed by independent sample *t*-test to compare the mean values between the different groups and Chi-square test for comparing proportion. $P \leq 0.05$ was considered statistically significant.

Results: Most of the study participants belonged to the age group of 21–30 years (mean 29.3 years, standard deviation 8.4 years). The male-to-female ratio was 1: 2.2. The majority of the patients in this study (27, 60%) were either overweight or obese. There was a statistically significant elevation in mean serum triglyceride level (TG) in CSU patients in comparison to normal controls ($P = 0.008$). Patients with a disease duration of more than 6 months had a significantly higher levels of non-high-density lipoprotein-cholesterol (non-HDL-C) ($P = 0.026$) and remnant cholesterol ($P = 0.038$), and significantly lower levels of mean low-density lipoprotein-cholesterol (LDL-C) ($P = 0.027$) and mean LDL/HDL ($P = 0.026$) in comparison to patients with a disease duration of 6 months or less.

Limitations: Small sample size and the cross sectional design were the main limitations.

Conclusion: Patients with CSU showed significantly higher levels of serum TG in comparison to controls. Patients with a disease duration of more than 6 months showed a significant increase in mean remnant cholesterol and non-HDL-C levels, and a significant decrease in LDL-C levels and LDL-C/HDL-C, when compared to those with a disease duration of 6 months or less.

Keywords: Chronic spontaneous urticaria, Serum lipid levels, Triglyceride, Non-high-density lipoprotein-cholesterol, Remnant cholesterol, Low-density lipoprotein-cholesterol

INTRODUCTION

Urticaria is a condition characterized by the development of wheals (hives), and/ or angioedema.[1] Based on the duration, it is classified as acute (upto 6 weeks) or chronic (>6 weeks) and further classified based on eliciting factors as spontaneous (no specific eliciting factor involved) or

inducible (specific eliciting factor involved).[1] The term "spontaneous" does not assume etiology, which may include autoimmunity, allergy, pseudoallergy, or infection.[2]

Experimental animal studies have found mast cells to be activated by pro-inflammatory mediators such as C3a, C5a, and oxidized low-density lipoprotein (LDL), and also to induce an atherogenic lipid profile and vascular inflammation, thereby promoting atherosclerosis.[3-6] Clinical trials have shown lipid-lowering drugs like statins to be effective in the treatment of chronic spontaneous urticaria (CSU).[7] In addition, a greater frequency of metabolic syndrome has been detected in patients with CSU compared to healthy controls.[8] Recently, Maged and Rushdy found statistically significant increase in serum cholesterol, triglycerides (TGs), and LDL-C (low-density lipoprotein-cholesterol), and decrease in high-density lipoprotein-cholesterol (HDL-C) in CSU patients in comparison to controls.[9] Dyslipidemia is implicated in the inflammatory mechanism of atherosclerosis associated with metabolic syndrome; a similar mechanism has been proposed for the pathogenesis of CSU as well.[10] The paucity of research in this area has prompted us to take up this study.

MATERIALS AND METHODS

The primary objective of this analytical cross-sectional study was to compare the serum lipid levels in patients with CSU with those in normal subjects. The secondary objective was to study the clinical profile of patients with CSU. Approval was obtained from the Institutional Research and Ethics Committees before starting the study. Individual study participant gave written, informed consent.

We included all clinically diagnosed patients with CSU above 18 years of age who attended our tertiary care center during the study period of 1 year (January 2020 to December 2020). We excluded, patients who were known cases of dyslipidemia or had diseases that could predispose to dyslipidemia such as diabetes mellitus, hypothyroidism, liver disease, chronic kidney disease, systemic lupus erythematosus, and endocrine disorders; patients on lipid-lowering agents such as statins and fibrates; patients on systemic corticosteroid therapy during the past 2 weeks; patients on drugs modifying serum lipid levels such as thiazides, anabolic steroids, estrogens, cyclosporine, and antipsychotics during the past 3 months, and pregnant or lactating women. Age- and gender- matched healthy adults (without any skin or mucosal lesions) were recruited as controls. Dyslipidemia, conditions that can precipitate dyslipidemia and treatment with lipid-modifying drugs were considered as exclusion criteria while recruiting controls as well.

The calculated sample size was 37 based on a previous study by Maged and Rushdy.[9]

Detailed history on demography, comorbidities, and clinical features was collected using a structured questionnaire. General examination was carried out and findings including vital signs, height, and weight were recorded and body mass index (BMI) was calculated as per standard norms.[11] A thorough dermatological examination was carried out and findings including, number, pattern, and distribution of lesions were recorded in detail. Systemic examination to rule out any associated disease and relevant investigations for disease evaluation were done. All patients were subjected to a serum lipid profile estimation after 12 hours of fasting, analyzed using Beckman Coulter Olympus AU 680 (automatic analyzer) in the department of biochemistry of our institution. The cut-off values for dyslipidemia were based on the latest international guideline (serum total cholesterol >200 mg/dl, TG >150 mg/dl, LDL-C >130 mg/dl, and HDL-C < 40 mg/dl).[12]

Data were entered into Microsoft Excel sheets. Statistical analysis was performed using a trial version of Statistical Package for the Social Sciences 18.0. Quantitative variables were expressed as mean and standard deviation. Qualitative variables were expressed as frequency and percentage. Independent sample t-test was used to compare the mean values between two different groups and Chi-square test was used for comparing proportions. $P \leq 0.05$ was considered statistically significant.

RESULTS

A total of 45 patients with CSU satisfying the inclusion criteria and who attended our center during the 1 year period and 45 normal age- and gender-matched controls were studied. The age of the patients ranged from 18 to 50 years, with a mean age of 29.3 years (standard deviation 8.4 years). Most of the patients belonged to the age group of 21–30 years (27, 60.0%) followed by 31–40 years (9, 20%). Among patients, 31 (68.9%) were females and 14 (31.1%) were males, with a male/female ratio of 1: 2.2. Most of the patients were professionals (14, 31.1%) followed by homemakers (12, 26.7%) and students (10, 22.2%). The majority of the patients (18, 40.0%) had a disease duration between 4 months and 6 months, with a mean duration of 5.9 ± 2.4 months. Comorbidities observed were systemic hypertension in 2 (4.4%) patients and bronchial asthma in 1 (2.2%). Majority of the patients (27, 60%) in this study were either overweight or obese. The data regarding BMI are given in Figure 1. In majority of the patients, the most common time of appearance of lesions was evening (19, 43.2%), while 11 study participants (24.4%) reported night as the common time of appearance of lesions. The salient clinical features are given in Table 1.

Among the 45 CSU patients, 23 had dyslipidemia which constituted 51.1% of the total and the remaining 22 patients (48.9%) had lipid profiles within the normal range. Among the normal subjects, 14 (31.1%) had dyslipidemia and 31 (68.9%) had lipid profiles within the normal range [Figure 2].

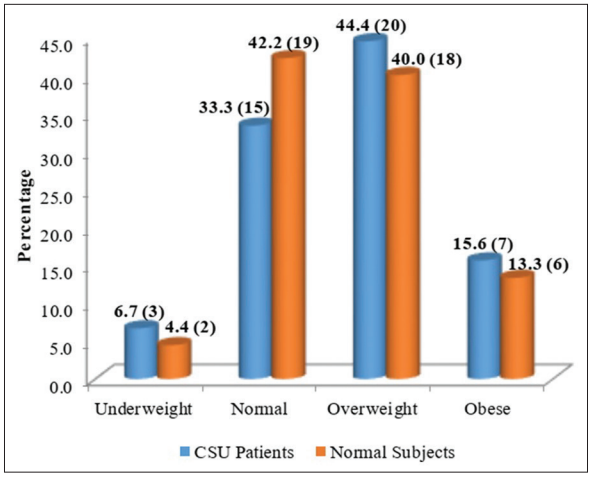

Figure 1: Bar graph showing classification of patients with CSU (chronic spontaneous urticaria) and normal controls based on body mass index (*n*=45). Number in brackets represents number of patients/ controls in each category.

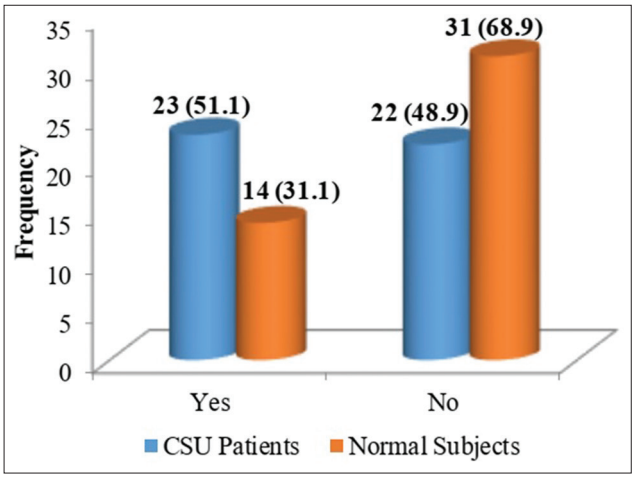

Figure 2: Bar graph showing dyslipidemia in CSU (chronic spontaneous urticaria) patients and normal controls. Number in brackets represents percentage of the total in each category.

No statistical significance was noted in the proportion of dyslipidemia between CSU patients and normal subjects (P = 0.054). The serum lipid profile of the study group and the comparison group is shown in Table 2. A statistically significant increase in mean TG level was observed in CSU patients when compared to normal subjects (P = 0.008). The changes in other lipid markers were not significant. Comparison of serum lipid profiles between CSU patients with a disease duration of 6 months or less and those with a duration of more than 6 months is shown in Figure 3. Mean non-HDL-cholesterol (non-HDL-C, 104.5 ± 28.7 mg/dl) and mean remnant cholesterol (51.1 ± 27.5 mg/dl) were significantly higher in patients with a disease duration of more than 6 months compared to those with a disease duration of 6 months or less (P = 0.026 and P = 0.038, respectively). Mean LDL-C and LDL-C/HDL-C were significantly lower in patients with a disease duration of more than 6 months (P = 0.026 and P = 0.027, respectively).

Table 1: Salient clinical features of patients with chronic spontaneous urticaria.

Clinical features	Frequency (Percentage) *n*=45(100%)
Disease duration	
6 months or less	22 (48.9%)
>6 months	23 (51.1%)
History of atopy	5 (11.1%)
Family history of urticaria	3 (6.7%)
Type of lesion	
Wheals	41 (91.1%)
Dermatographism	4 (8.9%)
Angioedema	6 (13.3%)
Distribution – predominant site	
Diffuse body involvement	20 (44.4%)
Upper limb	15 (33.3%)
Lower limb	6 (13.3%)
Trunk	3 (6.7%)
Face	1 (2.2%)

DISCUSSION

The present study included 45 patients with clinical diagnosis of CSU and an equal number of age- and gender-matched normal controls. The most common age group (21–30 years) and the mean age of the patients were comparable to most other studies on CSU.[13-15] However, a slightly higher age group of 31–40 years was documented as the common age group in a few studies.[9,16]

The majority of the patients in this study were women (68.9%) which was in concordance with similar studies by Maged and Rushdy and Dharani *et al.*[9,15] Among the study participants, only three had coexisting illness (systemic hypertension in two patients and bronchial asthma in one). Krupashankar *et al.* and Joseph *et al.* found diabetes mellitus as the most common co-morbidity in patients with CSU, followed by hypertension and bronchial asthma.[13,17] We had defined diabetes mellitus as an exclusion criteria since it is identified as a cause of secondary dyslipidemia. The presence of hypertension in these patients may further increase the risk of atherosclerosis.

Most of the patients in the study were either overweight/obese (60%) according to BMI, but no significant difference in BMI was noted between cases and controls. However, a previous study by Shalom *et al.* reported a significant association between CSU and higher BMI.[18] The mean disease duration, clinical presentation, and distribution of the wheals as observed by us were consistent with literature.[13,15,17]

Table 2: Comparison of serum lipid levels (in mg/dl) in CSU patients and normal controls.

Serum lipid	CSU patients		Normal subjects		*t*-test	*P*-value
	Mean	SD	Mean	SD		
Total cholesterol	196.2	26.2	194.0	22.8	0.43	0.672
Triglycerides	142.7	28.3	128.8	19.9	2.69	0.008
LDL-C	103.3	22.6	97.6	22.8	1.20	0.232
HDL-C	52.7	7.9	53.3	8.5	0.35	0.729
Non-HDL-C	95.6	27.8	96.6	22.5	0.19	0.852
Remnant cholesterol	42.9	27.3	43.3	22.7	0.80	0.937
LDL-C/HDL-C	2.0	0.5	1.9	0.7	0.71	0.476
TC/HDL-C	3.8	0.7	3.8	0.8	0.27	0.785

LDL-C: low-density lipoprotein-cholesterol; HDL-C: high-density lipoprotein-cholesterol; Non-HDL-C: non-high-density lipoprotein-cholesterol, TC: Total cholesterol, CSU: Chronic spontaneous urticaria

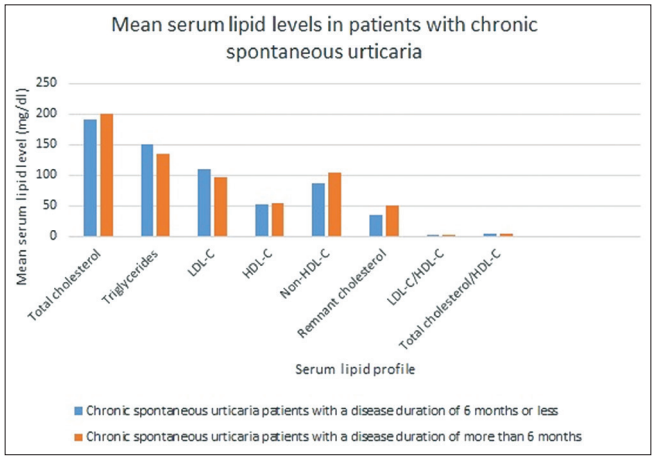

Figure 3: Bar graph showing serum lipid profile in chronic spontaneous urticaria patients with a disease duration of 6 months or less and a disease duration of more than 6 months. LDL-C: low-density lipoprotein-cholesterol, HDL-C: high-density lipoprotein-cholesterol, Non-HDL-C: non-high-density lipoprotein-cholesterol.

The significant increase in serum TG levels in patients with CSU (in comparison to the controls) was the most important finding in this study as our primary objective was to detect serum lipid abnormalities in CSU. These findings were concordant with the aforementioned study by Maged and Rushdy.[9]

We observed no significant difference between the mean levels of serum total cholesterol, LDL-C, and HDL-C in CSU patients and normal controls. These findings were discordant with the observations of Maged and Rushdy, who noted a significant difference in mean total cholesterol ($P < 0.001$), LDL-C ($P < 0.001$), and HDL-C ($P = 0.004$) between patients and controls. Mean non-HDL-C and remnant cholesterol levels did not show a significant difference between cases and controls in our study. The LDL-C/HDL-C and total cholesterol to HDL-C ratio, which are considered as predictors of cardiovascular risk, were not significantly different between the cases and controls.

In addition to being the major cell mediator in urticaria, mast cells are also implicated in atherosclerosis. Mast cell granule remnants can bind to LDL to form larger particles that are scavenged by macrophages and smooth muscle cells, thereby enhancing LDL-C uptake for foam cell formation in atherosclerotic plaque.[4]

Mast cells also secrete tryptase, which can degrade pre-beta-HDL. As HDL particles can remove cholesterol from the macrophage and transport it back to the circulation, inhibiting the production of mature HDL through mast cell tryptase can impair reverse cholesterol transport and may promote the development of atherosclerotic lesions.[5]

Mast cells, which are part of the innate and adaptive immune systems, have also been found to cause endothelial inflammation, which is a major step in the development of atherosclerosis.[6]

Thus, the inflammatory mechanisms in CSU and dyslipidemia-induced atherosclerosis may be closely related.

The mean level of TG was lower in patients with disease duration of more than 6 months compared to those with disease duration of 6 months or less, though not statistically significant ($P = 0.083$). This was again in contrast with the observation of Maged and Rushdy, who found a significant positive correlation between serum TG levels and disease duration ($P < 0.001$). The mean LDL-C was found to be lower in patients with disease duration of more than 6 months compared to patients with disease duration of 6 months or less, and the difference was significant ($P = 0.027$). However, in contrast with our study, Maged and Rushdy found significantly higher serum LDL-C levels in patients with longer disease duration ($P < 0.001$). The significant elevation noted in mean non-HDL-C and remnant cholesterol in patients with a disease duration of more than 6 months (in comparison to those with a shorter disease duration), as observed by us, may have ominous implications since remnant cholesterol is now known to be associated with cardiovascular risk.[19] The possibility of a pathogenic role for remnant cholesterol, especially in longstanding CSU should be investigated in larger trials.[19] In most of the standard laboratories, the level of remnant cholesterol is not calculated and mentioned, and this should be particularly estimated due to the aforementioned importance of this particular type of cholesterol. The mean level of HDL-C was higher in patients with a disease duration of more than 6 months compared to patients with a disease duration of 6 months or less, but this was not significant ($P = 0.563$). Maged and Rushdy also found no significant association between serum HDL-C levels and

disease duration ($P = 0.360$). Though mean total cholesterol level was elevated in patients with a disease of longer duration, the difference was not significant. This was in contrast with the previously reported study, where serum total cholesterol levels showed a significant positive correlation with the disease duration ($P < 0.001$).[9] The mean LDL-C/HDL-C was significantly lower in patients with a disease duration of more than 6 months ($P = 0.026$), whereas the mean TC/HDL-C showed no association with disease duration. These two parameters were not analyzed by Maged and Rushdy.[9] The discordant results noted between our study and the study by Maged and Rushdy could be attributed to the higher mean age of the participants in the latter study (21-30 years and 31-40 years, respectively), as lipid abnormalities are expected to manifest more frequently with advancing age. In addition, the sample size was small in both studies. The study by Maged and Rushdy was done in Egypt, hence, the effect of genetic variations on the lipid profiles of the studied populations can not be ruled out. Moreover, remnant cholesterol and non-HDL-C were not measured by Maged and Rushdy, which were the lipid parameters that showed significant changes in our study.[9]

Limitations of the study

The major limitations of this study were the small sample size and the cross-sectional design.

CONCLUSION

Dyslipidemia was present in more than half of the CSU patients, and there was a statistically significant increase in mean serum TG levels in CSU patients compared to normal subjects. Mean non-HDL-C and remnant cholesterol levels were significantly higher and LDL-C levels and mean LDL/HDL were significantly lower in patients with a disease duration of more than 6 months compared to patients with a disease duration 6 months or less. This highlights the importance of assessing serum lipid levels, including remnant cholesterol and non-HDL-C, in patients with severe or uncontrolled CSU, as this can help improve the clinical outcomes and the quality of life of the affected. Prompt intervention can also reduce the risk of subsequent cardiovascular events. Lipid-lowering agents could play a role in the management of CSU in future. After a thorough literature search, we could not find any similar studies from India. Hence, we recommend future studies with large sample size.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

Financial support and sponsorship

Nil.

Conflicts of interest

Dr. Sukumaran Pradeep Nair and Dr. Anuja Elizabeth George are on the editorial board of the Journal.

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How to cite this article: Viswanath V, Mathew R, Nair SP, George AE. Serum lipid levels in chronic spontaneous urticaria – An analytical cross-sectional study from a tertiary care center. J Skin Sex Transm Dis 2023;5:98-103.