ОЦЕНКА ЛИПИДНОГО ПРОФИЛЯ ПРИ ХРОНИЧЕСКОЙ СПОНТАННОЙ КРАПИВНИЦЕ

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Резюме. Хроническая крапивница имеет рекуррентное течение, характеризуется зудом, эритемой, отеками слизистых оболочек в течение большей части недели на протяжении 6 недель или более. Есть предположение о том, что уровни и состав липидов крови могут вносить вклад в развитие или обострение крапивницы. Целью данной работы было исследование связи между хронической крапивницей и липидным составом крови. 50 пациентов с хронической крапивницей и 50 здоровых лиц были включены в исследование типа «случай-контроль». У пациентов с крапивницей проводилась оценка каждого параметра липидного профиля крови и тяжести крапивницы в 4 отдельных возрастных группах с учетом половых различий. Степень тяжести заболевания анализировали в связи с уровнями липопротеинов высокой плотности, липопротеинов низкой плотности, триглицеридов и холестерина. Уровни триглицеридов ($p = 0,039$), общего холестерина ($p = 0,031$) и липопротеинов низкой плотности ($p = 0,001$) были значительно выше у больных с крапивницей, нежели в контрольной группе. Не выявлено корреляций между тяжестью крапивницы (по шкале UAS7), возрастом и полом пациентов. Тяжесть крапивницы не различалась при сопоставлении с отдельными параметрами липидного профиля. Показано, что средние значения липопротеинов высокой плотности у больных с хронической крапивницей различного возраста существенно повышены у женщин по сравнению с мужчинами ($p < 0,002$). В нашем исследовании обранужена корреляция между наличием хронической крапивницы и гиерлипидемией. На основании этих данных можно рекомендовать исследование на гиперлипидемию у пациентов с хронической крапивницей.

Ключевые слова: гиперлипидемия, хроническая крапивница, липидный профиль сыворотки крови

EVALUATION OF LIPID PROFILES IN PATIENTS WITH CHRONIC SPONTANEOUS URTICARIA: A CASE-CONTROL STUDY

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Abstract. Chronic urticaria is referred to recurrent, pruritic, erythematous, and edematous mucocutaneous lesions on most days of the week, and persists for six weeks or more. There is a hypothesis about the levels

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of blood lipid profiles in CSU, which may have a contributing role in development or exacerbation of hives attacks. The present study was conducted to investigate the association between chronic urticaria and blood lipid profiles. Fifty patients with chronic urticaria and fifty healthy people were included in this case-control study. In chronic urticaria patients, each parameters of blood lipid profile and urticaria severity were evaluated in each of four age and two sex cathegories. Urticaria severity in chronic urticaria patients, was also analyzed for levels of HDL, LDL, Triglyceride and Cholesterol. Levels of triglyceride (p value = 0.039), total cholesterol (p value = 0.031), and LDL (p value = 0.001) were significantly higher in chronic urticaria patients than in control group. No correlation was found between the urticaria severity (UAS7 score) average, and the age and sex of the patients. Urticaria severity showed no significant difference within each lipid profile parameter. Average values of lipid profiles in patients with chronic urticaria in different age and sex showed that HDL has remarkably higher mean quantitation in women than men ($p < 0.002$). Our study found a correlation between chronic urticaria with hyperlipidemia. According to this investigation, we can advise that patients with chronic urticaria should be evaluated for hyperlipidemia.

Keywords: hyperlipidemia, chronic urticaria, serum lipid profile

Introduction

Urticaria is characterized by pruritic, erythematous, and edematous mucocutaneous lesions. One of its most important characteristics is that these lesions wax and wane rapidly. Urticaria can be classified into two groups based on its time duration. Acute urticaria lasts less than six weeks and chronic urticaria referred to recurrent lesions on most days of the week that persists for six weeks or more [1, 2, 3]. Chronic urticaria may significantly alter the patient's quality of life and causes impairment of daily life activities. chronic urticaria is estimated to exert influence on about 1.8% of the general population [5, 6], with a higher prevalence in middle-aged women [3].

While Several factors regarding the pathogenesis of idiopathic CU were known to be responsible (e.g. stress, food allergies, and autoantibody production against immunoglobulin E (IgE) receptor [4] ,The exact mechanism of chronic urticaria has not been understood yet. some immunologic cells such as mast cells and basophil cells have the central pathophysiologic role, and Autoimmune mechanisms in mast cell activation are thought to trigger spontaneous urticaria [7, 8, 13]. As we know, chronic spontaneous urticaria is an inflammatory disease described with infiltration of T cells, neutrophils, eosinophils, and cutaneous mast cell degranulation; as well as Increased levels of pro-inflammatory cytokines such as interleukin (IL)-6, tumor necrosis factor , matrix metalloproteinase (MMP)-9, and C-reactive protein (CRP) [10, 11, 12].

Some data are reported about previously coexistence of hyperlipidemia and metabolic syndrome in Chronic Urticaria [9]. Metabolic syndromes are the combination of dyslipidemia, obesity, high fasting blood sugar, and hypertension. Studies in which elevated levels of inflammatory markers such as IL-1, IL-6, TNF, and CRP illustrate pro-inflammatory states, are associated with metabolic syndromes [14, 15]. There is an imbalance between pro-inflammatory and anti-inflammatory adiponectin measures in patients with chronic urticaria [16]. Adiponectin is a biomedical mediator secreted by adipose tissue. It is important for inflammation, energy homeostasis, and cell proliferation. Any adipose tissue dysfunction may lead to adverse tissue secretion, metabolic syndrome, and skin inflammation [17]. In one study, metabolic syndrome was more prominent in refractory chronic urticaria cases than in healthy controls [10]. Several studies showed association between dyslipidemia and allergic diseases, but the results were contradictory [18, 19, 20]. It can be hypothesized that the levels of blood lipid profiles may be associated with the development or exacerbation of hive attack. So, if there is a connection between them, it may be possible to prevent the occurrence or relief the severity of the disease by proper treatment of hyperlipidemia and change in a patient's diet. Therefore, because of insufficient data on relationship between lipid profiles and chronic urticaria, current study was conducted to clarify the possible association between chronic urticaria and blood lipid profiles.

Materials and methods

In a case-control study, Patients and control groups were randomly selected. Studied population were matched for sex and age in both case and control groups, and none of the participants was smoker, or with a BMI>25, with a patent food or drug induced allergy or already diagnosed autoimmune disease. Those with underlying metabolic diseases such as obesity, hypothyroidism, rheumatologic disorders, and a history of hyperlipidemia were also excluded. Fifty patients with the diagnosis of chronic urticaria were enrolled in the study as case group from 2018 till 2020. Patients were diagnosed by a subspecialist in allergy and clinical immunology based on the definition of chronic urticaria according to standard European Academy of Allergology and Clinical Immunology/ the Global Allergy and Asthma European Network (EAACI/GA2LEN) guidelines [2] at their ambulatory care visits. The diagnosis of Chronic Urticaria was considered if the wheals last for 6 weeks or longer at

least 2 times a week and with unidentified underlying cause. patients' medical information was collected using a self-made questionnaire. Also, we determined atopic patients (atopic dermatitis, allergic rhinitis, or bronchial asthma) based on history and physical examination in both groups. The control group consisted of 50 healthy people without chronic urticaria who were matched with the case group in terms of age and gender.

The blood levels of triglyceride, total cholesterol, LDL and HDL were checked after 14 hours of fasting for both case and control groups.

The information from the two groups was compared with each other. Urticaria severity was evaluated based on the Urticaria Activity Scale questionnaire (UAS7) for patients. Patients were categorized as mild, moderate, and severe urticaria based on UAS7 score (mild = 0-15 wheals/24 hour, moderate = 16-27 wheals/24 hour, severe = 28-42 wheals/24 hour). People who did not want to enter the research project and did not complete the questionnaire were excluded from the study. The obtained information was entered in the SPSS version 21 software and analyzed with suitable statistical methods, including descriptive statistics methods (frequency indices and relative percentages) and appropriate statistical tests (chi-square test, independent T-test, and paired T-test). The significance level was considered at 0.05.

Results

In this study, the variation range of age in patients with chronic urticaria was 7-76 years. The average age was 33.36±13.86. Among these patients, 33 (66%) and 17 (34%) persons were female and male, respectively. Among the people with chronic urticaria, 21 people (42%) had a history of atopic disorders (atopic dermatitis, allergic rhinitis, or asthma) compared to 5 people (10%) with a history of atopic diseases in the control group. Twenty-five people (50%) also had a history of angioedema with urticaria in the patients group. Results of the study showed that the mean severity of urticaria based on UAS7 criteria in patients with chronic urticaria is 23.42 with a standard deviation of 12.96. The average UAS7 score was higher in females than males (24.73 *vs* 20.88) but the association was not considerable (p value = 0.32). Moreover, there was no significant difference between age and severity of urticaria (p value = 0.312), Although the UAS7 score was higher in the 3rd and 5th decades of life (Table 1).

Among these patients, 18 (36%), 8 (16%) and 24 (48%) persons had mild, moderate, and severe urticaria respectively. The lipid profiles were compared in both groups; and levels of triglyceride, total cholesterol and LDL were significantly higher in case than control groups. HDL level was lower in chronic urticaria group than control, but it was not indicating for a significant relationship (Table 2).

In this study, we also evaluated lipid profile levels in patients with different urticaria severity. As it is shown in (Table 3).

The different levels of triglyceride, total cholesterol, LDL and HDL in different severity groups were not significant. No significant relationship was found between total cholesterol, triglyceride and LDL levels and the gender of patients with chronic urticaria. However, serum cholesterol levels were significantly higher in female patients (p value = 0.002). No significant relationship was seen comparing serum lipid profile in patients of different age groups (Table 4). It should be noted that the standard deviation in some categories is very high; this is due to the high dispersion of triglyceride levels in this study.

TABLE 1. SEVERITY OF CHRONIC URTICARIA IN AFFECTED PEOPLE ACCORDING TO GENDER AND AGE

Gender / Age	USA7 score average	Number	p value
Male	20.88	17	0.320
Fmale	24.73	33	
< 20 years	17.2	8	0.312
20-29 years	26.6	12	
30-39 years	22.2	21	
≥ 40 years	27.4	9	

TABLE 2. COMPARING THE LIPID PROFILES IN CASE AND CONTROL GROUPS

Lipid profiles	Patients with chronic urticaria	Control group	p value
Total cholesterol	179.34±42.50	164.00±25.56	0.031
Triglyceride	119.20±80.85	94.32±23.65	0.039
LDL	107.5±25.3	81.68±8.57	0.001
HDL	47.90±12.01	50.06±8.86	0.309

TABLE 3. AVERAGE OF LIPID PROFILES AND URTICARIA SEVERITY

Urticaria severity	Cholesterol level Mean±SD	Triglyceride level Mean±SD	LDL Mean±SD	HDL Mean±SD
Mild	168.27±33.90	112.11±50.50	101.35±26.04	48.00±10.11
Moderate	210.8±72.1	177.2±165.2	117.37±32.07	51.50±18.01
Severe	177.80±31.08	105.17±48.10	108.80±22.01	46.60±11.25
Total	179.34±42.50	119.2±80.8	107.5±25.3	47.90±12.01
p value	0.06	0.08	0.31	0.61

TABLE 4. AVERAGE VALUES OF LIPID PROFILES IN PATIENTS WITH CHRONIC URTICARIA AND THEIR RELATIONSHIP WITH AGE AND SEX

Age (year) / Gender	Total cholesterol Mean±SD	Triglyceride Mean±SD	LDL Mean±SD	HDL Mean±SD
< 20	151.50±35.27	101.63±53.49	95.00±26.70	40.50±10.48
20-29	185.00±46.18	104.17±36.00	103.08±20.04	54.25±16.28
30-39	184.24±49.90	134.38±111.80	110.95±28.30	47.33±9.90
≥ 40	185.11±25.54	119.44±57.02	116.48±2082.00	47.33±7.81
p value	0.25	0.687	0.312	0.08
Female	179.7±37.6	110.76±50.03	107.48±26.12	51.61±12.60
Male	178.65±52.08	135.59±120.76	107.35±24.40	40.71±6.37
p value	0.93	0.3	0.99	0.002

Discussion

Chronic urticaria is a debilitating condition with important effects on quality of life. It is associated with anxiety, psychosocial disorders, depression, hypertensive diseases, lipid metabolism disorders, allergic rhinitis, and insomnia [21, 22]. Serum lipids and fatty acids may correlate with chronic urticaria. unsaturated fatty acids (ω3, ω6) and lipid peroxidases are possible risk factors for the onset of chronic urticaria [23]. In our study, we investigated the association between chronic urticaria and dyslipidemia. Fifty patients with chronic urticaria were included in this study and compared with 50 in healthy individuals. We showed that hyperlipidemia (delineated as high cholesterol, LDL and triglyceride) is more frequent in chronic urticaria patients than healthy people). Similar with our research in the study of Maged Amin [24], forty patients with chronic urticaria and healthy individuals were included, and their results were compatible with our findings. All lipid profiles (total cholesterol, LDL, HDL, and triglyceride) in the case group had significant differences with the control group. In Maged Amin's study, Total cholesterol, LDL, and triglyceride levels were higher in patients group, and HDL level was higher in the healthy group [24]. In another nationwide survey by Chung [25], adult patients with chronic urticaria were compared with healthy individuals in one case-control study. They investigated the significance of the differences in demographic characteristics such as geographic region, atopic disorders, autoimmune diseases, and urbanization levels between the two groups of patients. Based on their findings, 43.8% of patients in the case group and 28.4% in the control group had a prior diagnosis of hyperlipidemia. Patients with chronic urticaria had a 1.65-fold increased risk of having a diagnosis of prior hyperlipidemia [25]. They highlighted the need to evaluation of hyperlipidemia in chronic urticaria. They did not measure blood lipid profiles, and data had been achieved by history and prior registration. In our study, we measured serum lipid profiles in both groups and then compared them with each other. In addition, we evaluated the chronic urticaria severity score by the UAS7 questionnaire and compared it with serum lipid profiles in patients with chronic urticaria. Finally, there was no significant correlation between severity and serum lipid levels. With the comparison of urticaria severity score with sex and age, we did not find any significant relationship between them, although UAS7 was higher in female gender and the age group ≥ 40 yrs. Among the chronic urticaria group, 21 people (42%) had a history of atopic diseases (allergic rhinitis, eczema, and bronchial asthma). There are conflicting findings about the correlation between chronic urticaria and atopic diseases. Inflammatory processes that occur in dyslipidemia, can induce an imbalance between anti and pro-inflammatory cytokines such as IL-10, IL-17, and IL-23 respectively [26, 27, 28]. The study of Manti and colleagues was performed on 23 children with dyslipidemia disorder, 26 children with dyslipidemia – atopy, and 22 healthy children. They detected serum pro-inflammatory cytokines (IL-17, IL-23), anti-

inflammatory cytokines, serum cholesterol (total cholesterol, HDL, LDL), and triglyceride levels affected by dyslipidemia or dyslipidemia-atopic conditions. Serum IL-10 level as anti-inflammatory mediator was significantly lower in the dyslipidemia-atopic group than in children showing exclusively dyslipidemia. But pro-inflammatory cytokines such as IL-17 and IL-23 were higher in dyslipidemia-atopic patients than in children showing exclusively dyslipidemia [20]. Hsien-Yi Chiu in one study investigated the association between chronic urticaria and atopic diseases (asthma, atopic dermatitis, allergic rhinitis) and some autoimmune disorders. There was the most strong association between Chronic Urticaria with Kawasaki disease (modified OR, 2.76: 95% CI 1.15-6.63) followed by Henoch-Sch nlein purpura, atopic dermatitis, systemic lupus erythematosus, allergic rhinitis, autoimmune thyroid diseases, Sj gren syndrome, inflammatory bowel disease, and asthma with lower adjusted Odds Ratio, respectively [29]. Some literature have declared the role of serum LDL concentration in asthmatic patients but more studies are needed for definitive results [30]. In a systematic review on 3458 asthmatic patients in twenty studies compared with 29,146 healthy individuals, The levels of total cholesterol and LDL were significantly higher in the case group but there was no correlation between the case and control group for HDL levels [31]. Takashi Kusunoki et al, evaluated the relationship between serum lipid levels and allergic sensitization. They suggested that hyperlipidemia probably is a risk factor for allergic sensitization, and early intervention in dietary regiment of children with atopia and allergy may be useful to prevent flare up of allergic disorders [19].

Conclusion

Several studies showed that abnormality in serum lipid profiles can induce many pro-allergic and pro-inflammatory mechanisms. As we know, chronic urticaria is an inflammatory condition with unknown etiology, so increased levels of serum lipid profiles may induce chronic urticaria or may affect the duration and severity of the disease. Our study alongside with some other studies, found a correlation between hyperlipidemia and chronic urticaria. According to this investigation, we can advise that patients with chronic urticaria should be evaluated for hyperlipidemia and some atopic diseases. on the other hand, prescription of anti-lipid agents aimed to control the symptoms of chronic urticaria can be hypothesized to be the subject for further studies. However, because of some limitations in the present study (for example a low number of cases and no measurement of an allergic and inflammatory mediator), we suggest more accurate and expanded research in this field.

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