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Original scientific paper

Imbalanced Concentrations of Serum Lipids and Lichen Planus

Melita Vukšić Polić[1,2], Maja Miškulin[3], Krešimir Šolić[4], Vera Plužarić[1], Miroslav Sikora[5] and Bruno Atalić[6]

[1] »J. J. Strossmayer« University, University Hospital Center Osijek, Clinic for Dermatology and Venereology, Osijek, Croatia
[2] »J. J. Strossmayer« University, School of Medicine, Clinic for Dermatology and Venereology, Osijek, Croatia
[3] »J. J. Strossmayer« University, School of Medicine, Public Health, Osijek, Croatia
[4] »J. J. Strossmayer« University, School of Medicine, Biophysics, Medical Statistics and Medical Informatics, Osijek, Croatia
[5] Health Centre Osijek, Osijek, Croatia
[6] University of Cambridge, Department of Public Health and Primary Care, Cambridge, United Kingdom

A B S T R A C T

The aim of this study was to analyze possible connection between the lichen planus and imbalanced concentrations of serum lipids and to evaluate the impact of various dietary regimes (used in the regulation of imbalanced concentrations of serum lipids) on the regression of lichen planus lesions. Research was conducted as a case-control study comprised of 72 patients with Lichen Planus and 30 participants from control group, treated at the Clinic for Dermatology and Venereology of the Clinical-Hospital Centre Osijek, Eastern Croatia, during 2010 and 2011. LP cases were diagnosed with both a clinical examination conducted by a dermatovenerology consultant and by patohistological diagnostic. Serum lipid levels (total cholesterol, LDL-cholesterol, triglycerides, HDL-cholesterol) were determined by the classic laboratory diagnostics in both investigated groups (LP patients and control group). The present study has confirmed that there is a strong connection between the imbalanced concentrations of one or more serum lipids (cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides) and the occurrence of LP which is important in the therapeutic approach to patients with this disease.

***Key words**: dyslipidaemia, high density lipoprotein cholesterol (HDL-cholesterol), triglycerides, low density lipoprotein cholesterol (LDL-cholesterol), Lichen Planus, diet for hypercholesterolaemia, diet for hypertriglyceridemia, diet for the mixed hyperlipidaemia, serums lipids, Croatia*

Introduction

Lichen Planus (LP) is a chronic inflammatory disease of skin and mucosa which is characterized by a broad spectrum of clinical manifestations[1]. Its prevalence in different populations is between 0.4% and 1.9%[2]. For example, it is 0.73% in Pakistan[3], while in the USA it is 1.0%[1]. It usually occurs in populations of 45 years and older with the predominance among females[2]. Its classical clinical appearance involves polygonal papules and purple plaques. Typical finding are »Wickham's striae« which are white lacy streaks seen during a physical examination or with a help of the dermatoscopy[4]. Lesions usually occur on limbs, more often on the inner wrists and on the dorsal sides of feet and hands; less often on trunk and other localizations like backs and genitals or scalp; while they are very rare on nails[1,5–7]. Oral Lichen Planus (OLP) involves lesions of oral cavity mucosa and occurs in even 70–77% patients with the skin manifestations[8]. Lesions of the oral form of LP, as opposed to skin type LP have the potential malignant transformation[9–11]. LP Diagnosis is based on the clinical appearance and histological findings. Histological findings of papules are typical for LP and they assume hyperkeratosis, irregular broadening of the granulomatous skin layer, disappearance of the basal skin layer, and acanthuses in the shape of saw teeth, with a localized infiltrate in the upper dermis[5]. LP aetiology is unknown, but it is currently believed that it based on some kind of immunological process mediated with the lymphocytes T[2,8,12,13], which prob-

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ably occurs as a response to an unknown antigen in the predisposed persons[13]. Other possible and suggested etiological factors include infective agents – both bacterial and viral (most surely hepatitis C virus); various drugs like angiotensin convertase (AC) – inhibitors, beta – blockers, nonsteroid antirheumatics, metildopa, penicilamin, and antimalarics; and other underlying autoimmune diseases, food allergies, immunodeficiencies, habits, traumas, stress, depression, anxiety, diabetes mellitus (DM), hypertension, neoplasms, and digestive disorders[1,8,14–20].

Due to the fact that its aetiology is unknown, LP therapy is unspecific and supportive, with no universal therapy guidelines[13]. Various authors have investigated a possible connection between LP and other skin and chronic disease[1,21,22]. Certain authors have pointed towards the possible connections between LP and Alopecia Aeratae, Vitiligo, Lichen Sclerosis, Lupus Discoideus and other skin diseases, while Hayashi et al. have connected LP with tymoma[23]. Other diseases brought into connection with LP are Laugier-Hunziker Syndrome, primary biliary cirrhosis, primary sclerotic cholangitis, ulcerous colitis, DM, and diseases of thyroid gland, especially hypothyroidism[1,16,23–25]. LP was also connected with the carbohydrate disorders in the epidermal cells, because it showed greater prevalence among the people with DM than in the general population[2,26]. Certain authors who have investigated the connection between LP and DM have suggested that there are actually two LP types: one with the metabolic and the other with the immunologic defect; both of which are connected with DM[27,28]. Research conducted in Germany during 1984 aimed at the investigation of the connection between LP and DM. It confirmed higher levels of serum cholesterol in 35.5% of LP patients and 17.5% of healthy controls. Observed difference between two groups was statistically significant[29]. During 2006 a group of Spanish authors described a possible connection between the lipid metabolism and the pathogenesis and the development of the OLP lesions. They have managed to discover the differences between the total and VLDL cholesterol serum levels between the LP patients and healthy controls which were of statistical significance[30]. The most recent study dealing with the LP problematic was conducted by Dreiher et al. in Israel during 2009 and managed to show the connection between dyslipidaemia and LP on the large number of the study participants[2]. Above presented studies have clearly pointed towards the connection between the imbalanced concentrations of serum lipids and LP, which together with the currently used less than perfect therapy, has motivated us to create our study in order to analyze the mentioned connection between LP and dyslipidaemia in a systematic way and to evaluate the possible therapeutic influence of the prescribed diets for the control of the imbalanced levels of serum lipids.

Patients and Methods

This study was designed as a typical case-control study[31,32].

Patients

Study involved 72 LP patients who have been diagnosed and treated for LP for the first time (incidental cases) at the Clinic for Dermatology and Venereology of the Clinical Hospital Centre Osijek during 2010 and 2011 (minimum sample was increased by 10% due to the dependant measurements) and the control group made of 30 patients without LP who were treated for other skin disease at the same ward during the same period of time. Age of participants was between 18 and 90 years, including both groups and both sexes. Study involvement criteria were: LP diagnosis (both clinical and histological) confirmed at the Clinic for Dermatology and Venereology and the Clinical Institute for Pathology and Forensic Medicine of the Clinical-Hospital Centre Osijek during 2010 and 2011. Residence of the study participants was in the Osijek-Baranja County. Controls involvement criteria were: hospitalisation for another skin disease, but not LP, at the Clinic for Dermatology and Venereology of the University Hospital Centre Osijek during 2010 and 2011; residence in Osijek-Baranja County; and age between 18 and 90 years. Criteria for exclusion from both LP and control groups were: liver diseases including hepatitis B and C (data acquired through anonymous questionnaire); therapy with statins (data acquired through anamnestic questionnaire); and diagnosed hypothyroidism (data acquired through anamnestic questionnaire).

Methods

LP cases were diagnosed with both a clinical examination conducted by a dermatovenerology consultant and

TABLE 1
PATIENTS WITH LP AND CONTROL GROUP OF PATIENTS ACCORDING TO THE VALUES OF SERUM LIPIDS AND ACCORDING TO THEIR AGE

	LP patients (N=72)	Control Group (N=30)	p
Age $\overline{X}$±SD	54.40±13.23	57.57±10.03	0.243*
Cholesterol $\overline{X}$±SD	6.00±1.22	5.97±1.08	0.898*
TCG Me (25–75%)	1.70 (1.21–2.38)	1.66 (1.26–2.31)	0.777†
HDL Me (25–75%)	1.38 (1.20–1.60)	1.32 (1.10–1.63)	0.620†
LDL Me (25–75%)	3.40 (2.91–4.20)	3.77 (3.30–4.30)	0.071†

*Student t-test, †Mann-Whitney U-test

by a pathological analyses conducted by a pathology consultant (biopsy and skin patohistological diagnostics).

Serum lipid levels (total cholesterol, LDL-cholesterol, triglycerides, HDL-cholesterol) were determined by the classic laboratory diagnostics in both investigated groups (LP patients and control group). Imbalanced concentrations of serum lipids (dyslipidaemia) were defined as high in the case of total cholesterol, LDL-cholesterol, and triglycerides; and as low in the case of HDL-cholesterol. Referral values were: <5.0 mmol/L for total cholesterol; <3.0 mmol/L for LDL-cholesterol; and <1.7, mmol/L for triglycerides for both sexes; and >1.0 mmol/L for HDL-cholesterol in men and >1.2 mmol/L for HDL-cholesterol in women. All study participants (LP patients and control group) were asked to fill the anonymous questionnaire. It was composed of questions on demographical data (age, sex, residence, education), anthropometric data (height, weight), anamnestic data on LP for the LP patients (family anamnesis, treatment), anamnestic data on other skin disease for the control group, and anamnestic data on chronic diseases for all participants. LP patients were evaluated at the enrolment into the study according to the following criteria: felling of itching, presence of papules, presence of LP characteristic lesions on the inner wrists and on dorsal sides of feet and hands, oral cavity mucosa, and some other possible areas (nails, genitals). All the LP patients who had higher than normal levels of the serum lipids during the enrolment examination were instructed how to keep a diet which corresponded to the imbalanced levels of serum lipids (diet for hypercholesterolemia, diet for hypertriglyceridemia, diet for the mixed hyperlipidaemia). They have also received corticosteroid unguents for a local use for maximum of ten days. First control examination was conducted after ten days and the LP patients with the balanced levels of serum lipids after the proposed diet were excluded from the study. Control examination was conducted after three months. The remaining participants had the clinical evaluation of their skin status and the laboratory control of serum lipid levels (total cholesterol, LDL-cholesterol, triglycerides, HDL-cholesterol). The condition of LP patients was defined as improved if the number of the disease positive criteria was reduced, as worsened if the number of the disease positive criteria was increased, or as unchanged if the number of the disease positive criteria stayed the same.

Prior to enrolment in the study, each participant was thoroughly informed on the objectives and purpose of the study, and gave his/her informed consent for inclusion. The study was approved by the Osijek School of Medicine Ethics Committee, and all procedures used in the study were performed in line with ethical standards, recommendations of the Osijek School of Medicine Ethics Committee and Helsinki Declaration provisions.

Statistics

The numerical data are presented with a mean and a standard deviation if normally distributed. If the distribution did not follow a normal pattern, the numerical data were presented with a median and an interquartile range[33]. Comparison between the independent groups was done with the Student t-test and the Mann-Whitney U-test, while the comparison between the repeated measures was done with the t-test for Dependent Groups and the Wilcoxon Signed Ranks test. Statistical calculations were conducted using the software package SAS 9.1 (SAS Institute INC, Cary, NC, US) with the significance level put at $\alpha = 0.05$.

Results

Results are presented in Tables 1 and 2 and Figure 1. The results of our study have shown that there was no statistically significant difference between the group of patients with LP and control group of patients according to the values of serum lipids and according to their age (Table 1). The results of our study have also shown that the regulation of the imbalanced concentrations of se-

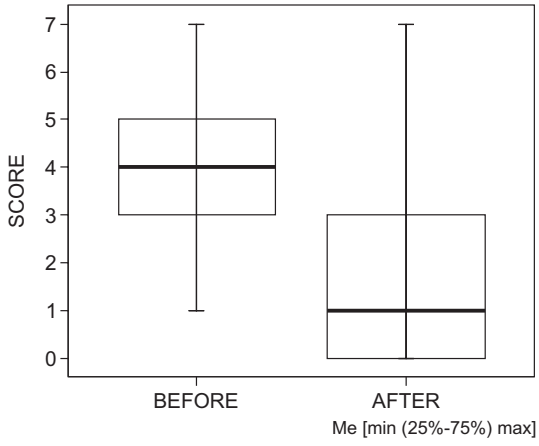

Fig. 1. Average value of positive symptom scores among LP patients before and after diet, p<0.001, Wilcoxon Signed Ranks test.

TABLE 2
DISTRIBUTION OF LIPIDS AMONG THE LP PATIENTS BEFORE AND AFTER THE SUGGESTED DIETS

Serum Lipids	LP patients before diet (N=72)	LP patients after diet (N=72)	p
Cholesterol Me (25–75%)	6.06 (5.40–6.90)	5.00 (4.90–6.03)	<0.001†
TCG Me (25–75%)	1.79 (1.35–2.43)	1.60 (1.32–1.92)	0.002†
HDL Me (25–75%)	1.36 (1.20–1.60)	1.40 (1.20–1.77)	0.625†
LDL $\overline{X}$±SD	3.65±1.15	3.23±0.85	<0.001*

*T-test for Dependent groups, †Wilcoxon Signed Ranks test

rum lipids with the mentioned diets resulted in statistically significant improvement in serum lipid levels in all cases, except in case of High density lipoprotein cholesterol (HDL-cholesterol), which values have also been improved after diet but observed difference before and after the diet was not statistically significant (Table 2). Finally, the results of our study have shown that among LP patients before and after the diet there was statistically significant difference in average value of positive symptom scores (Figure 1).

Discussion

The results of our study have shown that there was no statistically significant difference between the group of patients with LP and control group of patients according to the average values of serum lipids. In this respect our results are in a disharmony with the results of the other authors, for example, Hornstein et al., who have determined the statistically significant difference between the levels of serum lipids among the LP patients and healthy controls[28]. Dreiher et al. have conducted a case-control study in which they have shown how the prevalence of a dyslipidaemia was higher among the LP patients than among the healthy controls, and this difference was also statistically significant[2].

The results of our study have clearly shown that the regulation of the imbalanced concentrations of serum lipids with the mentioned diets leads towards the improvement of the clinical signs of LP, which represent a novel approach in therapy of this disease and which further strongly confirms the connection between the imbalanced concentrations of serum lipids and LP that Dreiher et al. have also shown in their study[2]. In their study, Dreiher et al. have managed to explain the observed connection on the cellular level as well. According to them LP is an autoimmune process. In this respect, they have highlighted a roll of the cytokines which are excreted from the T lymphocytes during the immunological reactions of delayed hyper-reactivity and whose roll is the regulation of the inflammatory cells which produce free oxygen radicals, which can then destroy keratinocytes. LP is thus characterized by a higher expression of the inflammatory CXCR3 ligands which are connected with the activation of the effector cytotoxic T lymphocytes and plasmid dendritic cells. Various cytokines, including interleukins (IL)-2, IL-4, IL-6, IL-10, tumour necrosis factor (TNF-α), interferon (IFN-a, IFN-c) and b1 growth transforming factor are included in the LP pathogenesis as well. On this track, they have proved that IFN-a was responsible for the induction of the induced CXCR3 ligands CXCL9, CXCL10 i CXCL11[2]. Dreiher et al. thus claim that the described inflammatory processes could explain the connection between LP and dyslipidaemia, and possibly the other components of the described metabolic syndrome as well, due to the fact that a chronic infection plays a significant role in its pathogenesis. As a proof for their hypothesis they state the proven fact of the higher activity of the type 1 helping lymphocytes T in the described metabolic syndrome, with a crucial role of cytokines IL-6 and TNF-α, and the observed connection between TNF-α inhibitors and higher levels of HDL-cholesterol[2].

Main advantage of our study is its prospective type, while the main disadvantage is relatively small number of participants. It should be highlighted that this study managed to prove the therapeutic influence of the diets directed towards lowering of the serum lipids on the regression of the LP skin lesions as well. The observed fact could be used as a starting point for the further researches of this enigmatic disease.

In conclusion, the present study has confirmed that there is a strong connection between the imbalanced concentrations of one or more serum lipids (cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides) and the occurrence of LP which is important in the therapeutic approach to patients with this disease. Bearing in mind the fact that cardiovascular and cerebrovascular disorders are the leading cause of mortality in Eastern Croatia[34], which, according to literature reports, can be favorably influenced by appropriate dietary habits the finding of this study is in public health sense even more important. Following this, one can through the dietary influence on LP symptoms also improve general health of the population and prevent the occurrence of various circulatory diseases. Such comprehensive approach that simultaneously prevents several diseases is even more important for Croatia, which is trying to optimize costs of health care of its citizens and stabilize its health system.

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M. Vukšić Polić

»J. J. Strossmayer« University, University Hospital Center Osijek, Clinic for Dermatology and Venereology, Huttlerova 4, 31 000 Osijek, Croatia
e-mail: melyderma@gmail.com

POREMEĆENE KONCENTRACIJE SERUMSKIH LIPIDA I LIHEN PLANUS

S A Ž E T A K

Cilj ovog istraživanja bio je analizirati moguću povezanost lihen planusa i poremećene koncentracije serumskih lipida te procijeniti utjecaj različitih dijetnih režima (korištenih u regulaciji poremećenih koncentracija serumskih lipida) na poboljšanje kliničke slike lihen planus. Istraživanje je bilo ustrojeno po načelima *case-control* studije u koju je bilo uključeno 72 bolesnika oboljelih od lihen planus i 30 kontrolnih bolesnika oboljelih od neke druge kožne bolesti, liječenih u Klinici za dermatologiju i venerologiju KBC Osijek, u istočnoj Hrvatskoj, tijekom 2010. i 2011. godine. Lihen planus je bio dijagnosticiran kliničkim pregledom od strane specijaliste dermatovenerologa i patohistološkom dijagnostikom. U obje skupine koje su sudjelovale u istraživanju (ispitanici i kontrole) klasičnom laboratorijskom dijagnostikom utvrđene su razine serumskih lipida (kolesterola, HDL-kolesterola, LDL-kolesterola i triglicerida). Provedeno istraživanje potvrdilo je da postoji jaka veza između poremećenih koncentracija jednog ili više serumskih lipida (kolesterol, HDL-kolesterol, LDL-kolesterol, trigliceridi) i pojave LP što je važno u terapijskom pristupu oboljelima od ove bolesti.