INTRODUCTION
The studying of the comorbidity of skin diseases is a priority scientific direction in modern dermatology. Understanding of the commonality of pathogenetic aspects, clinical alertness and timely diagnosis of comorbid conditions allow to conduct individual rational treatment aimed at the treatment of dermatosis associated with comorbid disorders. It is known that comorbid conditions are exactly aggravate the course of the underlying disease leading to chronicization of the process, disability of patients. Understanding of the commonality of pathogenesis and the mutually complicating nature of comorbidity makes a possible to prescribe individual rational treatment.

THE AIM
The aim of the study was search and analysis of the data of review, experimental and clinical scientific and medical publications on the issues of the comorbidity of LP.

MATERIALS AND METHODS
Searching was carried out through the PubMed/MEDLINE portal from the databases of the National Center Biotechnology Information, U. S. National Library of Medicine, National Institute for Health and Clinical Excellence, as well as the portals «Scientific Electronic Library eLIBRARY.RU», «Russian Science Citation Index (RSCI)» and «Index Copernicus».

Conclusions: The main global trends of comorbidity of LP are determined. The results of these studies can form the basis for updating of clinical guidelines for the management of patients with LP at the international and local levels.

KEY WORDS: comorbid conditions, lichen ruber planus, rational treatment
The viral hepatitis C is one of the most well-known associations of LP, and its comorbidity with the oral LP (OLP) is considered a postulate. The HCV seropositivity has been recorded in 16 % of patients with LP and in 6 times more frequently with oral form of dermatosis in comparison with control group. [11]. However, in 2017, a group of Indian scientists has published the results of a survey of 84 patients with a histopathologically verified diagnosis of lichen planus. The patients have been examined for the presence of hepatitis B and C, in all 84 cases the results have been negative. The revealed zero comorbidity allowed the authors to conclude that screening patients with LP on viral hepatitis B and C is unjustified, at least in the Indian population. [12]. The comorbidity of LP with chronic active hepatitis, biliary cirrhosis, and dyslipidemia have been also noted in earlier single studies. Some associations have been confirmed later by more extensive researches. Thus, a meta-analysis of 7 observational studies with a total of 5242 subjects revealed an association of LP with dyslipidemia, which occurred 1.74 times more often than in the control group. At the same time, lipid metabolism disorders were manifested by an increase in the level of triglycerides, low-density lipoproteins, total cholesterol and a decrease in the level of high-density lipoproteins. [13]. According to the authors, it is necessary to screen lipid metabolism parameters when establishing the diagnosis of LP. Concomitant hyperlipidemia may also worsen the prognosis for recovery in LP patients. The epidemiological study conducted in Singapore demonstrated that patients who suffer on LP associated with hyperlipidemia and / or diabetes mellitus showed a significantly lower degree of improvement after treatment compared with a group of patients without such comorbidities. [9, 13].

A high degree of comorbidity of the OLP with pathology of the gastrointestinal tract and the hepatobiliary system (76.5 %), disorders of the nervous system (70.5 %), cardiovascular system (61.8 %) was found in a small core study (47 patients) by a group of scientists from the Ural Scientific Research Institute of Dermatology and Immunopathology. The dermatosis was less associated with endocrine pathology (44.1 %), chronic viral diseases (38.2 %) and diseases of the genitourinary system (34.5 %). Moreover, the poly-systemic comorbid pathology was most often recorded in patients with erosive-ulcerative form of LP [14].

In recent years, new data on comorbid associations of LP with autoimmune diseases have been appeared. There was no statistically significant difference in the combination of the OLP and autoimmune diseases, since the identified association of 7 % did not significantly differ from the same indicator of the control group (4 %) [15]. The cutaneous form of the LP (CLP) has demonstrated such an association in an recent extensive study of Thai scientists. A study of 12,427 patients suffering from LP has shown a reliable association of dermatosis with systemic lupus erythematosus (multivariate odds ratio (mOR) was 2.87) with Sjögren’s syndrome (mOR = 3.75) with dermatomyositis (mOR = 6.34) with vitiligo (mOR = 2.01), with alopecia areata (mOR = 2.82). The identified associations, according to the authors, need further study and researching of the mechanisms underlying them, as well as analyzing the role of autoimmunity in the etiology of LP. [16].

A study of the comorbidity of LP with scleroticrophic lichen has been also conducted. The authors evaluated the histopathological characteristics of vulvar biopsies of 31 patients (mean age 69.5 years) with the vulvar form of the LP and the current scleroticrophic lichen of the vulva preceding or simultaneous, and also described the clinical features of the comorbidity of these conditions. 30 samples demonstrated a pathological picture of erosive LP, moreover, 22 samples with elements localized on the inner surface of the labia minor and 8 ones localized on the mucous membrane of the vaginal opening. The overlay of scleroticrophic lichen on the LP was detected in 3 (10 %) patients. The most significant pathological marker of the identified association was the pattern of regeneration of the basal layer characteristic of the LP. According to the authors, the combination of genital lichen planus and scleroticrophic lichen is not rare. However, the association of these dermatoses is not sufficiently diagnosed due to the lack of a characteristic histopathological picture, pathomorphologic errors in the case of the “overlap syndrome” of lichens, as well as different localization of foci of various dermatoses requiring multiple biopsies. The authors of the study revealed a pattern of lichen-comorbid lesions on the vulva, in which the LP is localized on the inner surface of the labia minor and the vaginal opening with scleroticrophic lichen foci on its periphery. Some crucial pathomorphological and clinical signs showing LP and scleroticrophic lichen association in vulva area was also noted. This research gave no answers about frequency of comorbidity of genital LP and scleroticrophic lichen, however, the proposed tools help to identify better such combinations. [17].

Chinese scientists Li D., Chen Q., Hua H. and co-authors researched 11 electronic databases of clinical studies which were published before August 2016. These researches were devoted to the problem of association of OLP and thyroid pathology. Eight researches were taken for the survey, four of them with case-control was included in the final meta-analysis. According to Newcastle-Ottawa scale, the
average score of four researches was 6.5, chance coefficient (CC) was 2.1 (confidence interval 95%). This was indicated a statistically significant difference in the prevalence of thyroid pathology in patients with OLP compared the control group. Two publications were showed a higher reliable correlation between OLP and hypothyroidism (CC=1.83). The author`s meta-analysis was demonstrated a significantly higher prevalence of thyroid disease among patients with OLP compared the control group, that indicates the need for screening such patients in order to identify thyroid pathology. However, more studies are required to confirm the results because of little amount of surveys involved in meta-analysis [18].

Another study was included 215 patients with OLP showed significantly high percentage of thyroid diseases, especially hypothyroidism, and authors assumed the comorbidity of these conditions [19]. The results of another research, published in 2017, were confirmed a possible connection between the severity of the OLP and serum autoantibodies titer to thyroperoxidase and thyroid pathology. A significant positive correlation between the serum levels of IL-8 and autoantibodies to thyroperoxidase was revealed. A significant increase of autoantibodies to thyroperoxidase level in blood of patients with the erosive form of OLP was detected. This can be an indicator of previously unrevealed thyroid pathology in these patients [20]. In a recent study of 549 patients suffering from thyroid diseases, the clinical manifestations of OLP were detected almost 3 times more often than in the control group. The need to inform endocrinologists about the possible association between oral mucosa lesion in LP and thyroid disorders was indicated [21].

It should be noted that the endocrine associations of LP are not limited to the pathology of the thyroid gland. A recent study by Indian dermatologists was detected 33 (33%) patients with diabetes of 100 patients with LP and it was confirmed by high fasting blood glucose level. Authors emphasized the need to screen blood analysis among people with lichen planus to control glucose level [22]. Authors indicated the need for screening a blood glucose test in patients with LP [22]. Comorbidity of LP and diabetes mellitus lowers clinical efficacy of dermatosis treatment, slowing recovery. The authors suggested that the inflammatory nature of components of metabolic syndrome plays a significant role in the pathogenesis of LP. Particularly, hyperglycemia inhibits the proliferation of keratinocytes and fibroblasts, causes endothelial cell apoptosis and reduces vasodilation by blocking the synthesis of nitric oxide. Furthermore, the final glycation products activate the NF-κB signaling pathway, resulting in the release of pro-inflammatory cytokines and intracellular oxidative stress [9, 22].

In our opinion, a study devoted to the study of psychosomatic disorders associated with LP is quite interesting as well. In a prospective clinical study of 93 patients with predominantly CLP (58 women, 35 men; mean age – 47.6 years) the authors identified following data: psychogenic manifestations of the skin process in 28 (30.1 %) patients; nosogenic reactions, which were qualified as an adaptation disorder – in 56 (60.2 %) of them, recurrent depression – in 9 (9.7 %), while stress as a trigger rarely was objective and significant. Depressive nosogeny, a greater extent, depended on the prevalence and severity of the skin process and were accompanied by anxiety-hypochondriac depressive reaction with decreased mood, irritability, tearfulness, sleep disorders, psychosomatic hyperesthesia phenomena contributing to the amplification of itch. Sociophobic reactions and reactions with the phenomena of hypochondria of beauty were mainly recorded in cases of localization of lesions in open areas of the body with moderate and minor severity of dermatosis. Recurrent depressions accompanied in all cases the classical course of the LP and manifested in depression, anguish, anxiety, and thoughts of hopelessness and feeling of own inferiority [23].

Iranian scientists studied the connection between OLP with psychological stress appearance. The authors studied 45 scientific papers for the period from 1985 to 2014, identified in the main bases for the following search subjects: “oral red lichen planus”, “stress”, “anxiety”, “depression”, “psychological disorder”. Only 10 works met the necessary requirements. In these studies they used questionnaire methods for assessing stress, evaluating genetic polymorphism at the DNA level, studying the level of hormones in the human body, and the effect of drug therapy of mental disorders on patients suffering from OLP. The criteria for inclusion in the study were clinical and histopathological confirmation of OLP, exclusion criteria – the uncertainty of the diagnosis, inadequate number of subjects in the experimental and control groups, discrepancy (mismatch) in sex and age between the main and control groups. The results of the meta-analysis showed that a higher level of stress was noted in patients suffering from the OLP. The reduction of psychological stress and the well-being of patients are important and must be considered during the treatment of LP [24].

In a comparative study conducted at Oral Medicine Clinical Services (OMCS) of the University of Washington, psychosomatic disorders were studied in patients with LP and oral lichenoid rash compared with healthy persons and with patients suffering from myofascial pain. The diagnoses were confirmed clinically and pathomorphologically. The SCL-90R and VAS tools were used to evaluate pain. From January 2011 to March 2017, scientists examined 112 patients with OLP. 40 patients with oral lichenoid rashes, 185 patients with myofascial pain and 90 healthy persons according to the inclusion/exclusion criteria. The study revealed the absence of a significant difference in the assessment of the SCL-90R scale results in patients with OLP and the control group however, there was a tendency to develop moderate and severe degree, compared with control group.

In patients with OLP, on average, higher rates of depression were observed compared with control, though the differences were not significant. High and moderate pain-related somatization was detected in 36 % of patients with OLP and 28 % ones with oral lichenoid rashes com-
pared with 23% in the control group, while moderately severe somatization without pain was significantly higher in the OLP group than in control. The results of the studies showed the need for psychosocial examination and assessment of the patient's status with OLP, as well as the rationality of including psychotherapy in a comprehensive treatment plan for this condition that can help improve the prognosis and quality of life [25].

Keeping in mind a long course of treatment for LP and often empirical therapeutic approaches, the understanding of the psychosomatic associations of LP is an important point in the interaction of the patient and the dermatologist and the key to successful therapy.

In the context of the psychosomatic nature of the LP, a group of Indian scientists carried out a psychometric assessment of the patient's status with OLP compared with the control group. The patients with LP showed significantly higher incidence of comorbid mental disorders (depression, anxiety and stress) compared with the control. The authors expressed the opinion that a psychiatric assessment can be entered into standard protocols for the treatment of OLP [26].

CONCLUSIONS
Analysis of the data of scientific and medical literature over the recent years has shown that the problem of comorbidity of LP remains the focus of the scientific interests of dermatologists of the international community. Most studies deal with the study of endocrine, psychosomatic and internal comorbidity. The results of the Indian study were detected zero comorbidity of LP and viral hepatitis B and C, although previously the association of hepatitis C and LP was considered a postulate and HVC serological screening was recommended by standard protocols for the management of patients with LP. Current regional Indian guidelines may call into question the need for this test. There were convincing results about the association of the ORP and thyroid pathology. Considering widespread thyroid disorders in Ukraine, there is a need to inform endocrinologists and dentists about the need for mutual cooperation and screening of these patients in order to identify thyroid pathology.

The previous hypotheses about comorbidity of LP with components of metabolic syndrome – diabetes mellitus and dyslipidemia were confirmed as well, their negative impact on the effectiveness of treatment of dermatosis was revealed and a screening examination of lipid metabolism indicators was recommended when managing patients with LRP. A large proportion of psychosomatic disorders identified in patients with CLP and OLP may initiate the introduction of psychiatric evaluation into standard protocols for the treatment of patients with LP.

REFERENCES


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