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Risk factors for lipid disorders in systemic lupus erythematosus

ABSTRACT

Systemic lupus erythematosus (SLE) is one of the autoimmune diseases of the connective tissue system with multi-organ involvement. Dyslipidemia in SLE results from the increased risk of cardiovascular diseases typical in the general population. Still, it is exacerbated by inflammation and medications (particularly glucocorticosteroids). In the course of SLE, lipid disorders are related to the disease activity and result from cardiovascular risk factors typical for the general population. During the therapy, it is recommended to control the lipid profile and modify the lifestyle risk factors (implement a properly balanced diet and appropriate physical activity). The role of immunosuppressive and immunomodulating therapy in SLE, which may have a pro-or anti-atherogenic effect, is also emphasized. Thus, the assessment of the dyslipidemia type in this disease is crucial. Proper hypolipemic treatment not only reduces the risk of cardiovascular disease but also affects the survival of patients.

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KEY WORDS: systemic lupus erythematosus; dyslipidemia; cardiovascular risk; hypolipidemic therapy

INTRODUCTION

Systemic lupus erythematosus (SLE) is one of several autoimmune systemic connective tissue diseases that has a rich clinical picture. The aetiopathogenesis of the disease is currently unknown, however, the involvement of genetic and environmental factors in its development is highlighted [1, 2]. Moreover, synthesis is observed of autoantibodies against specific cellular components, mainly antinuclear antibodies [2, 3]. SLE most commonly involves the skin, joints and kidneys, however, cardiovascular, respiratory, nervous system and even bone marrow symptoms may also occur. The course of the disease can be mild or rapid with periods of remission and exacerbation [3, 4]. The incidence of SLE is estimated to range from 25–39 cases per 100 000 individuals in Europe per year. In Poland, approximately 20 000 individuals are affected by SLE. Women suffer from the disease nine times more often than men, and the peak incidence is observed between 16 and 55 years of age [5–7].

Lipid metabolism disorders are considered the most common determinant of cardiovascular diseases (CVD) in Poland [5, 8, 9]. Furthermore, dyslipidemia develops in SLE itself, which is due not only to the ongoing inflammatory process but also to iatrogenic complications [e.g., glucocorticosteroids (GCS) used] [11–13]. Hence, SLE needs regular monitoring of the lipid profile and additional preventive measures such as lifestyle modification regarding both dietary behaviour change and physical activity [8–10].

In view of the above-mentioned data, this study describes numerous risk factors for the development of lipid disorders in SLE and possible methods for their prevention and treatment.

LIPID DISORDERS IN SLE THAT ARE NOT RELATED TO DISEASE ACTIVITY

Dyslipidemia is a heterogeneous disorder with complex molecular mechanisms. Most of the factors that increase the risk of this dis-

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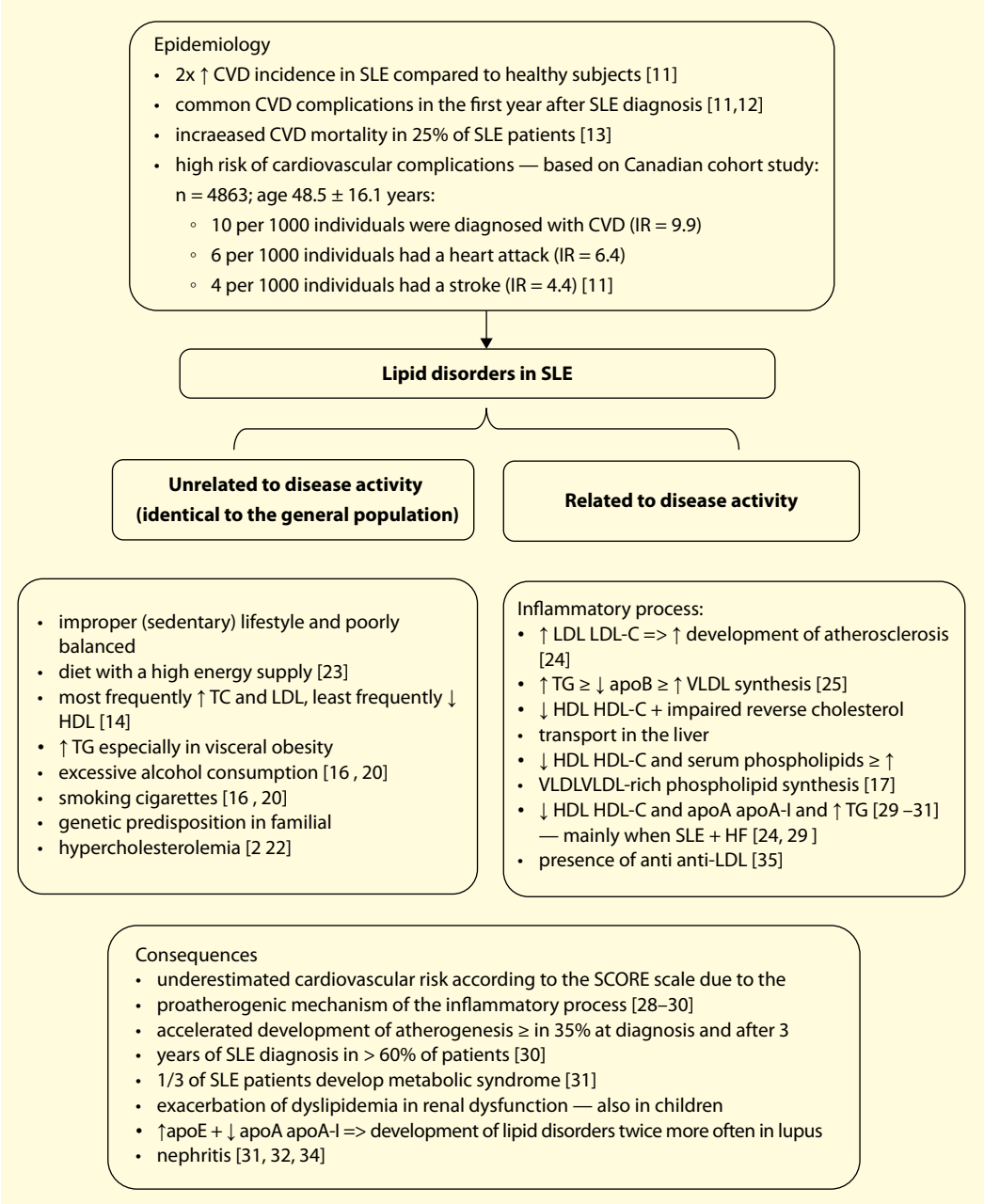

Figure 1. Epidemiology and characteristics of lipid disorders in SLE patients. ApoA-I — apolipoprotein A-I; ApoB — apolipoprotein B; ApoE — apolipoprotein E; CVD — cardiovascular disease; HDL-C — high-density lipoprotein cholesterol; HF — heart failure; IR — incidence rate; LDL-C — low-density lipoprotein cholesterol; SLE — systemic lupus erythematosus; TG — triglyceride

order are secondary, dependent on lifestyle, diet, or pharmacotherapy (Fig. 1). The most common lipid disorder found in patients before initiation of hypolipemic therapy is elevated total cholesterol (TC), and low-density lipoprotein cholesterol (LDL-C) levels. The least common disorder is low high-density lipoprotein cholesterol level (HDL-C) [14]. Hypercholesterolemia (defined as an increase in TC and/or LDL-C levels or an increase in non-HDL-C levels) occurs in 34–51% of SLE patients [15]. On the other hand, hypertriglyceridemia is most commonly diagnosed in patients with abdominal obesity and a sedentary lifestyle [16].

The occurrence of chronic inflammation in many diseases (not only rheumatic diseases but also in obese patients) has the additional effect of reducing HDL-C levels and impairing cholesterol reverse transport. The decrease in serum levels of HDL-C and phospholipids results in compensatory changes, including increased synthesis of phospholipid-rich very low-density lipoprotein (VLDL) [17]. As a result, atherosclerosis and metabolic syndrome develop in chronic inflammation [18].

Modifiable factors for the occurrence of this disorder, in addition to an improperly balanced high-energy diet, include excessive alcohol consumption. Hence, patients diagnosed with elevated triglyceride (TG) levels are advised to eat a well-balanced diet with a reduction in the intake of simple sugars (sweets). A high-carbohydrate diet containing significant amounts of simple sugars or refined carbohydrates and low in dietary fibre may cause a transient increase in TGs and a decrease in HDL-C. Furthermore, simple sugars with a high glycaemic index and/or high glycaemic load may cause an increase in serum TGs [19].

In cases of hypertriglyceridemia, alcohol intake should be reduced at the same time (< 10–20 g/day for women and < 20–30 g/day for men) [16, 20]. VLDLs are the main carrier of TGs, and their increased synthesis is an independent risk factor for CVD. High levels of VLDL particles were found to correlate with the risk of myocardial infarction [21].

Another modifiable risk factor for the development of CVDs that is unrelated to SLE is smoking. It has an adverse effect on lipid profile values. In addition to increasing TC, TG and LDL fraction levels, it causes a decrease in HDL-C. Moreover, nicotinism increases the atherogenicity of LDL lipoproteins [16, 20].

Non-modifiable risk factors for lipid disorders in SLE, in addition to sex and age of the patient, include genetic conditions, especially those leading to the development of familial hypercholesterolemia. It is caused by autosomal mutations of the LDL receptors, resulting in increased levels of this fraction [22].

Since appropriate lifestyle modification has a significant influence on individual lipoprotein values, it is essential to ensure proper education for SLE patients and encourage them to make lifestyle changes such as reducing body weight, being physically active, eating a well-balanced diet, quitting smoking and abstaining from excessive alcohol consumption [23].

LIPID DISORDERS IN SLE THAT ARE RELATED TO DISEASE ACTIVITY

Due to the increased risk of atherosclerosis and inflammatory activity in SLE, there is an increased cardiovascular risk. This is illustrated in Aviña et al. [12] study involving 4863 SLE patients in Canada, 86% of whom were women aged 48.5 ± 16.1 years. That group of patients, according to the authors, was diagnosed with CVD, myocardial infarction and stroke (Fig. 1). As a result, there was a twofold higher incidence of CVD in SLE compared to those without the disease [11]. Furthermore, SLE patients are most likely to develop cardiovascular complications in the first year after diagnosis [11, 12]. This is illustrated by Bernatsky et al. [6], who published the results of a large cohort study (n = 9547) on CVD mortality in SLE patients. Those results revealed that approximately 313 out of 1255 deaths were due to CVD. This indicates the need for increased cardiac vigilance in those patients, especially as the timing of SLE is related to reproductive age (3rd and 4th decades of life), in which pregnancy itself and especially the postnatal period may be associated with an increased risk of SLE exacerbation, including the occurrence of complications related to cardiac and vascular diseases [13].

In SLE, an increased inflammation is related to augmented HDL-C levels [24]. If concomitant hypertriglyceridemia is observed, there is a degradation of apoB synthesised in the liver and a reduction in its levels, which induces VLDL synthesis [25]. Studies in CVD patients without SLE imply that the ratio between serum lipid-associated proteins (apolipoproteins) — ApoB: ApoA1 determines CVD risk more effectively than routine cholesterol measurements. A higher ApoB/ApoA1 ratio was found to be associated with increased cardiovascular risk [26, 27].

As inflammation and dysfunction of vascular endothelium in SLE significantly increase the risk of atherosclerotic lesions, it is important to estimate cardiovascular risk, i.e., the risk of death from CVD (e.g., coronary artery disease or atherosclerosis) or a sudden cardiovascular incident (myocardial infarction) [28]. Hence, the calculated risk according to the SCORE (Systematic Coronary Risk Evaluation) scale that is recommended for cardiovascular risk assessment in rheumatic patients may be underestimated due to the proatherogenic mechanism of the inflammatory process. This has the effect of underestimating the risk of developing CVD [29, 30]. It has been proved that in SLE there is a decrease in HDL-C and apolipoprotein A-I (ApoA-I) levels and an increase in TG levels [29–31]. These abnormalities are particularly prevalent in SLE patients with coexisting heart failure (HF), in whom significantly lower HDL-C and ApoA-I levels are observed compared with SLE patients without HF [24, 29]. The severity of HF in SLE patients can significantly affect TC, TG and LDL-C levels [28, 29].

As already mentioned, the increased lipid deposition and increased connective tissue inflammation in SLE accelerate atherosclerotic processes. This is well illustrated by statistics that show that one-third of patients are diagnosed with dyslipidemia in SLE at the time of diagnosis, and this figure doubles three years after diagnosis [30]. Moreover, more than 30% of SLE patients have metabolic syndrome [31].

Furthermore, dyslipidemia in SLE is exacerbated by renal disorders. In lupus nephritis (without coexisting diabetes), there is an increase in TC and TG levels, including in children. This leads to an increase in TG levels and a decrease in HDL cholesterol, and these changes occur in nearly 60% of children after diagnosis of SLE. Moreover, lipid disorders develop twice as often in the presence of impaired renal excretory function and are most severe in nephrotic syndrome [31–33]. Levels of apolipoprotein E (ApoE) increase with disease activity, and levels of the anti-atherosclerotic cholesterol transport protein (apoA-I) decrease with disease activity [34]. The described changes are responsible for the increased proportion of patients with dyslipidemia in SLE, both in adults and children [31, 32].

A factor that further contributes to the increased risk of heart disease in SLE is the higher prevalence of anti-lipoprotein lipase antibodies. Anti-lipoprotein lipase antibodies occur in dyslipoproteinemia and are associated with increased SLE activity. Higher values of ESR, CRP and high activity as determined by the SLEDAI (Systemic Lupus Erythematosus Diseases Activity Index) scale are then observed. These changes are more often accompanied by the presence of anti-dsDNA and anti-cardiolipin antibodies [35].

To summarise the above data, it should be noted that SLE patients with normal serum lipid levels assessed by standard methods often have subclinical CVDs. Hence, CVD risk is usually underestimated by standard assessment methods. Therefore, to identify patients at high CVD risk in the SLE patient population, more sensitive and specific lipid markers need to be determined.

NON-PHARMACOLOGICAL TREATMENT

DIET

Obesity is one of the modifiable risk factors for dyslipidemia in SLE (body mass index ≥ 30 kg/m^2. The highest risk of lipid disorders is observed in the case of abdominal obesity defined by waist circumference: ≥ 94 cm in men and ≥ 80 cm in women [29]. Weight reduction in the obese was found to affect favourable changes in the serum lipid profile, as it positively lowers the levels of the LDL-C fraction and TGs [36].

The primary dietary recommendation in SLE patients is to reduce the intake of simple carbohydrates (especially sweets and sugary fizzy drinks). Diet therapy should be rich in vitamins and mineral substances (mainly with antioxidant potential). At the same time, it is recommended to reduce the intake of saturated fats and increase the proportion of unsaturated fatty acids (mono- and polyunsaturated, including essential fatty acids). These acids have anticoagulant and anti-atherogenic effects. The normalisation of body weight and normolipidemia achieved by such recommendations protects tissues from damage and inhibits the systemic inflammatory process [37, 38].

Furthermore, in dyslipidemic patients, attention is paid to the consumption of foods rich in phytosterols (sunflower and pumpkin seeds, sesame seeds, legumes, products with plant sterols, e.g. yoghurts and margarine). These compounds inhibit the absorption of cholesterol from the gastrointestinal tract and thus have a hypolipemic effect. They mainly cause a reduction in TC and LDL-C levels [39, 40].

In SLE patients, not only is a well-balanced diet important to minimise the risk of CVD but also the contribution of selected nutrients, including vitamins, which have a beneficial effect on lipid metabolism. Such vitamins include, for example, niacin (vitamin B3), which influences the reduction of TG and LDL-C levels by approximately 20% in adults with SLE and in 30% of children with coexisting dyslipidemia in SLE. On the other hand, no significant contribution of niacin to changes in HDL-C levels was proved [38]. The lipid profile is also favourably influenced by one amino acid – taurine found in animal products, which reduces serum LDL-C lipid levels [39].

Fibre is an important nutrient that plays a significant role in the dietary therapy of lipid disorders. Due to its low energy density, fibre reduces the calorific value of the diet and has a beneficial effect on lowering the level of the LDL-C fraction in SLE patients. It also increases HDL-C levels [39, 40]. Recent reports have also emphasised the beneficial contribution of vitamin D, adequate levels of which are associated with a low risk of CVDs. Unfortunately, vitamin D deficiency is often observed in SLE patients. This is due to low sunlight exposure

as a result of photosensitivity and renal insufficiency, in the course of which decreased calcitriol synthesis is observed. Many reports emphasise the positive effect of vitamin D not only on bone metabolism in SLE patients but also on processes of vascular endothelial regeneration, which significantly prevents CVDs in this patient group [41–44].

PHYSICAL ACTIVITY

Physical activity, in addition to a balanced diet, is one of the most important methods of maintaining the proper body weight [45]. For SLE patients with chronic joint and muscle pain (arthralgia and myalgia), physical activity should be adapted to the patient's mobility capabilities [46]. Due to the need to use energy resources for regenerative processes, physical effort is temporarily not recommended in severely ill patients with very active disease activity; however, as the general health status improves, it is necessary to include exercise aimed at preventing disability and minimising the risk of developing obesity and thus developing severe lipid disorders and CVD. Unfortunately, patients with high disease activity and multi-organ involvement in SLE are more likely to lead a sedentary lifestyle compared to patients with a mild course of the disease or patients in remission. Motivating SLE patients to adopt an active lifestyle (individually tailored to the patient's capabilities) is a primary goal of intervention programs run by foundations uniting SLE patients. Unfortunately, many patients do not take up any exercise after a relapse, often making excuses for their underlying disease [47]. Activity-based management of patients not only improves their performance but also has a beneficial effect on generating an anti-inflammatory response in the body as evidenced by increased synthesis of cytokines such as interleukin 10 (IL-10) [48].

Chronic joint pain is a significant difficulty in maintaining physical activity in SLE. In addition to arthralgia, pain complaints may affect other organs, and the pain itself may be generated by inflammatory processes within the serous membranes and the accumulation of large amounts of fluid within the pericardium, pleura and peritoneum. Persistent pain affects the deterioration of mental status and is associated with a significant risk of depression and chronic fatigue syndrome [49]. On the other hand, active leisure activities have a beneficial effect on the mental state of patients [50].

The impaired cardiovascular fitness and muscle strength in SLE compared with the general population may promote a sedentary lifestyle [9]. Unfortunately, reduced physical activity in SLE, in addition to the typical adverse changes in lipid profile, generates the synthesis of pro-inflammatory HDL-C, which affects the activation of atherosclerotic plaques in the carotid arteries [51].

According to the literature, aerobic exercise may improve cardiovascular fitness and function [54]. Consequently, therapeutic exercise intervention reduces the risk of cardiovascular complications in SLE [51, 53].

PHARMACOLOGICAL TREATMENT OF SLE AND THE RISK OF DYSLIPIDEMIA

Pharmacological treatment of SLE patients is individual, according to the degree of disease activity and organ damage [36, 54]. High disease activity may be responsible for an increased risk of dyslipidemia; hence the underlying disease must be properly treated [54, 55]. The main medications for SLE are antimalarial drugs (AMDs) such as hydroxychloroquine or chloroquine. In mild SLE (without organ damage), symptomatic treatment of e.g. joint and muscle pain or depressed mood is used in addition to AMDs [56, 57]. In SLE with moderate disease activity, patients usually need low- to medium-dose GCSs in addition to AMDs. AMDs are drugs with pleiotropic effects and reports in recent decades have emphasised their beneficial effects on lipid disorders [58]. Regular ophthalmological follow-up is recommended to monitor the adverse effects of AMDs and GCS [41, 42, 59, 60]. In addition, long-term use of GCS in SLE influences the occurrence of lipid disorders and the development of insulin resistance. On the one hand, these drugs lead to a decrease in disease activity but on the other hand, they cause many metabolic disorders and increase the risk of numerous cardiovascular complications [43, 44].

Immunosuppressants include azathioprine, cyclophosphamide, mycophenolate mofetil, and cyclosporin A [59], and their use requires constant monitoring for possible adverse effects [60]. Despite their effect on reducing disease activity, and thus normalising the lipid profile, some drugs may adversely affect individual cholesterol fractions. The effects on lipid metabolism are shown in Table 1.

Table 1. Effects of drugs for systemic connective tissue diseases on lipid disorders in SLE patients

Effects of drugs on lipid disorders in SLE patients		
Drug group	**Effects on lipid metabolism**	**Recommendations**
GCS (prednisone, prednisolone, methylprednisolone)	• FFA metabolism disorders • lipolytic effect • ↑ TG, VLDL, LDL • ↓ HDL [61]	• lipid profile control • implementation of hypolipemic therapy • lifestyle modification (well--balanced diet, appropriate physical activity)
Azathioprine	• ↑ TG • ↓ HDL [61] • ↑ calcification in vessels • ↑ development of atherosclerosis [62]	
Cyclosporine A	• ↑ TG, VLDL, LDL • ↓ HDL [63] • binds strongly to the LDL receptor (more so than tacrolimus) [62] • ↓ activity of metabolic pathways + ↑ risk of obesity • ↓ cholesterol transport into the bile [62, 63]	
Hydroxychloroquine or chloroquine	↓ TC, TG, VLDL, LDL [64]	

FFA — free fatty acids; GCS — glucocorticosteroids; HDL — high-density lipoprotein; LDL — low-density lipoprotein; TG — triglycerides; VLDL — very low-density lipoprotein

HYPOLIPEMIC TREATMENT FOR DYSLIPIDEMIA IN SLE PATIENTS

The primary aim of treatment for dyslipidemia is to reduce LDL-C levels in the first place. Modification of the other cholesterol fractions should occur only after the target LDL-C level has been achieved [18, 20]. Statins are the main drugs that are used in hypercholesterolemia. They inhibit 3-hydroxy-3-methylglutaryl coenzyme A. Coenzyme A is the main enzyme involved in cholesterol synthesis and results in a reduction in LDL fraction levels by up to 30–60% from the initiation of pharmacotherapy. At the same time, there is a decrease in TG levels by approximately 20–45% while the HDL cholesterol fraction increases by approximately 5–15%. Moreover, statins also show beneficial anti-inflammatory and anticoagulant effects [64, 65].

The second group of drugs are fibrates (fibric acid derivatives), which are agonists of the nuclear receptor peroxisome proliferator-activated receptor alpha. Fibrates are responsible for lipid metabolism. Their action is based on an increase in lipoprotein lipase activity and an effect on fatty acid oxidation, resulting in a reduction in serum TG levels. There is an increase in the levels of ApoA-I and ApoA-II, which leads to a process of HDL lipoprotein synthesis. In addition, fibrates have anti-inflammatory and anticoagulant effects [16].

Ezetimibe is a drug that inhibits the NPC1L1 (Niemann-Pick C1-Like 1) protein that is involved in controlling intracellular cholesterol transport in the epithelial cells of the initial segment of the jejunum. Inhibition of this protein reduces cholesterol absorption by approximately 50%. This results in an increase in the density of receptors for LDL-C in the liver, which increases the uptake of LDL lipoproteins. By inhibiting the absorption of dietary cholesterol in the small intestine, cholesterol delivery to the liver is reduced. Combination therapy involving the combination of a statin with ezetimibe is an increasingly common therapy for the treatment of dyslipidemia. Ezetimibe further lowers TG levels while causing an increase in HDL-C fraction [16, 66].

SUMMARY

Lipid disorders are the most common determinant of CVDs in Poland. In SLE, they are additionally exacerbated by the ongoing inflammatory process and iatrogenic complications (e.g., use of GCS). Not only are hypolipemic drugs important in the treatment of dyslipidemia in SLE but also drugs that reduce the activity of the underlying disease. A well-balanced diet minimising the risk of CVDs and an active lifestyle leading to normalisation of body weight are important. Lipid disorders should be treated according to current guidelines of the Polish Cardiac Society and the European Society of Cardiology. As some drugs used in the treatment of SLE may affect lipid disorders, it is important to systematically monitor the lipid profile in SLE patients.

CONFLICT OF INTEREST

None declared.

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