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METABOLIC EFFECTS OF STATINS: RISK OF DIABETES MELLITUS

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Abstract: Statins are a group of medications prescribed to lower blood cholesterol levels and prevent cardiovascular disease. This article reviews current understanding of the mechanisms of action and clinical efficacy of statins. Data on the safety of therapy are presented, including the risk of developing type 2 diabetes mellitus and factors influencing its occurrence. It is emphasized that the benefits of statins outweigh the potential risks with a rational and individualized approach to treatment.

Key words: statins, diabetes mellitus, cholesterol, dyslipidemia, lipid metabolism, LDL.

Метаболические эффекты статинов: риск развития сахарного диабета (Обзор литературы)

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Аннотация Статины – представляют собой группу лекарственных препаратов, назначаемых для снижения уровня холестерина в крови и профилактики сердечно-сосудистых заболеваний. В статье рассмотрены современные представления о механизмах действия и клинической эффективности статинов. Представлены данные о безопасности терапии, включая риск развития сахарного диабета 2 типа и факторы, влияющие на его возникновение. Подчёркивается, что польза применения статинов превышает возможные риски при рациональном и индивидуализированном подходе к лечению.

Ключевые слова: статины, сахарный диабет, холестерин, дислипидемия, липидный обмен, ЛПНП.

Statinlarning metabolik ta'siri: Qandli diabet xavfi

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Annotatsiya: Statinlar qon xolesterin miqdorini pasaytirish va yurak-qon tomir kasalliklarining oldini olish uchun buyuriladigan dorilar guruhidir. Ushbu maqolada statinlarning ta'sir mexanizmlari va klinik samaradorligi haqidagi hozirgi tushunchalar ko'rib chiqiladi. Terapiya xavfsizligi haqidagi ma'lumotlar, jumladan, 2-toifa diabet rivojlanish xavfi va uning

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paydo bo'lishiga ta'sir qiluvchi omillar keltirilgan. Davolashga oqilona va individual yondashuv bilan statinlarning foydasi potentsial xavflardan ustun ekanligi ta'kidlangan.

Kalit so'zlar: statinlar, qandli diabet, xolesterin, dislipidemiya, lipid almashinuvi, LDL.

Introduction. Cardiovascular diseases are widespread worldwide, including in Uzbekistan, with lipid metabolism disorders being a key cause. Men are significantly more likely to die from myocardial infarction than women. Furthermore, a significant proportion of cardiovascular diseases are caused by arterial hypertension (58.4% and 57%, respectively). A prospective study conducted in Uzbekistan to determine the prevalence of hypertension revealed that among deceased individuals, its incidence was 65.2% in men and 60.2% in women. It has been established that in the last decade, men and women aged 20–59 in Uzbekistan have been more susceptible to high blood pressure. Moreover, behavioral risk factors such as smoking, dyslipidemia, stress and poor nutrition play an important role in the development of hypertension, against which background the proportion of coronary heart disease also increases [4].

Overall, the increasing prevalence of cardiovascular disease in the 20th and 21st centuries is largely due to changes in modern lifestyles. Key factors include an increasingly fast-paced lifestyle and increased stress, physical inactivity, poor nutrition, disrupted work-rest schedules, unhealthy habits (alcohol, smoking, drugs), and the unnecessary use of pharmaceuticals [3].

Against this backdrop, dyslipidemia has become particularly significant as a key modifiable risk factor. Dyslipidemia is any disorder of lipid metabolism that results in elevated blood lipid levels, including total cholesterol (TC) (≥240 mg/dL [6.20 mmol/L]), low-density lipoprotein (LDL) cholesterol (>160 mg/dL [4.13 mmol/L]), triglycerides (TG) (>200 mg/dL [2.25 mmol/L]), or low high-density lipoprotein (HDL) cholesterol (<40 mg/dL [1.03 mmol/L]).

According to research, dyslipidemia affects 13% of the US population and is a predictor of various cardiovascular diseases (CVD). In the US, more than 100 million adults over 20 years of age have total cholesterol levels ≥200 mg/dL (≥5.17 mmol/L), and nearly 31 million have levels ≥240 mg/dL (≥6.20 mmol/L). However, less than 50% of patients with high TG and LDL-C levels receive treatment, and only 35% of them achieve adequate control of their cholesterol and TG levels [1].

It should be noted that atherogenic dyslipidemia is also common among patients with non-alcoholic fatty liver disease and is detected in 20–80% of patients.

The high prevalence of cardiovascular disease and the significant role of dyslipidemia in its development necessitate further study of this issue.

The purpose of the work: the objective of this work is to study and summarize current data on the use of statins in clinical practice, evaluate their effectiveness in the prevention of cardiovascular diseases, and analyze the safety of therapy, including the risk of developing type 2 diabetes.

Materials and Methods: The authors of this study reviewed and analyzed literature from the last 5-10 years of scientific publications using the search engines cyberleninka.ru, elpub, and GOOGLE ACADEMY and SCIENCE-EDUCATION using the above-mentioned keywords.

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Main part. Statins are a group of medications used to lower low-density lipoprotein (LDL) levels, also known as "bad" cholesterol, and prevent cardiovascular disease. Their mechanism of action involves inhibiting the enzyme HMG-CoA reductase, which plays a key role in cholesterol synthesis. A decrease in intracellular cholesterol levels in hepatocytes leads to an increase in the number of LDL receptors on their surface. This promotes more active uptake and removal of LDL from the bloodstream, which, in turn, reduces plasma cholesterol concentrations [5].

HMG-CoA reductase is the main enzyme regulating endogenous cholesterol synthesis. Statins reduce LDL cholesterol levels and moderately increase high-density lipoprotein (HDL) cholesterol (by 5-10%), especially at low baseline levels. The effect on triglyceride (VLDL) levels is usually minor, amounting to approximately 10%. The primary lipid-lowering effect is associated with a reduction in total cholesterol due to the LDL fraction. The relationship between drug dose and LDL reduction is exponential: doubling the dose results in an additional reduction in LDL concentrations by approximately 6% (the "rule of six"). Statins also reduce apolipoprotein B production and are considered the "gold standard" for the treatment of atherogenic dyslipidemia. [7] In addition to their lipid-lowering effect, statins have a number of additional (pleiotropic) properties: they improve endothelial function, reduce C-reactive protein levels, inhibit platelet aggregation, and suppress smooth muscle cell proliferation [5].

The high efficacy of statins in the treatment of hypercholesterolemia has determined their leading role in modern cardiology practice, especially in the context of primary and secondary prevention of cardiovascular complications [7].

Pharmacotherapy should be combined with non-drug measures, including a balanced diet (e.g., a Mediterranean diet), regular physical activity (at least 150 minutes per week), smoking cessation, and weight management. However, in some cases, lifestyle changes alone are insufficient, necessitating the use of medications, including statins.[1]

Despite their proven clinical efficacy, the possible link between statin therapy and the development of type 2 diabetes has been the subject of intense debate in recent years. This side effect was discovered significantly after the widespread use of statin therapy. It is suspected that the lipophilicity of the drugs may be a contributing factor, but the precise mechanisms remain poorly understood.

According to existing data, statins can inhibit the synthesis of ubiquinone (coenzyme Q10), leading to decreased ATP production and impaired insulin secretion by pancreatic β-cells. Results from clinical trials are mixed: for example, the HOPE-3 study, which involved 12,700 patients, found no increase in the incidence of diabetes. Meanwhile, a meta-analysis of 13 randomized trials (91,140 participants) showed a small but statistically significant increase in the relative risk of type 2 diabetes of 9%.

The absolute increase in risk remains minimal—approximately 0.4% over 4 years of therapy (corresponding to one additional case per 250 patients). It has also been established that the risk increases with increasing dose: with high doses, it is 12% higher than with medium doses [6].

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The likelihood of developing diabetes during statin therapy is largely determined by the patient's baseline metabolic status. Risk factors include prediabetic conditions (insulin resistance, impaired glucose tolerance), as well as the presence of metabolic syndrome components and treatment parameters (duration and intensity). As the number of metabolic syndrome components (obesity, hypertension, hypertriglyceridemia, low HDL levels, and hyperglycemia) increases, the likelihood of developing new cases of diabetes increases. Thus, in a study involving 8,749 men with metabolic syndrome without diabetes (of whom 2,142 received statins) aged 45–73 years, intensive therapy was associated with a 46% increase in the risk of diabetes (11.2% vs. 5.8%; $p < 0.001$) over 5.9 years, corresponding to approximately 10 cases per 1,000 patients annually.

To date, it remains controversial whether the diabetogenic effect of statins is general across the entire class or specific to individual drugs. Proposed mechanisms include increased insulin resistance, decreased insulin secretion, dysfunction of pancreatic β-cells and mitochondria, and decreased expression of the glucose transporter GLUT4 and caveolin-1. Further support has been obtained from studies using Mendelian randomization: an association has been established between the rs17238484 allele of the HMGCR gene and increased blood insulin (1.62%, 95% CI 0.53–2.72) and glucose (0.23%, 95% CI 0.02–0.44).

However, there is evidence that the diabetogenic effect is not inherent to all representatives of this class. In particular, pitavastatin demonstrates a neutral effect on glycemic control in both diabetic and nondiabetic patients [2]

Conclusion: In conclusion, statins are effective in lowering LDL levels and preventing cardiovascular disease. Despite a slight increase in the risk of developing type 2 diabetes, their benefits significantly outweigh potential side effects. Statin use should be individualized and combined with lifestyle modifications.

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