Effects of COVID-19 and diabetes mellitus on apolipoprotein A1 level in the blood plasma

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Summary

Background. Increased levels of high-density lipoprotein cholesterol (HDL-C) and apolipoprotein A1 (ApoA1) in plasma is associated with a reduced risk of developing cardiovascular diseases (CVD). In addition to its potential cardioprotective function, HDL and ApoA1, the main HDL apolipoprotein, also have antidiabetic properties.

Aim. The aim of the study was to determine the level of ApoA1 in the blood of patients (n = 81) with diabetes mellitus and COVID-19.

Methods. ApoA1 was determined by enzyme-linked immunosorbent assay (ELISA) kits (Elabscience, USA). The measurements were performed at an optical wavelength of 450 nm.

Results. ApoA1 level in the blood of patients with diabetes and especially with COVID-19 was significantly lower than in the blood of healthy people.

The study of the dependence of the content of ApoA1 in blood plasma on the level of Hb1Ac, the gender of patients and the type of diabetes showed that in blood of patients with type 2 diabetes the amount of ApoA1 is lower than in patients with type 1 diabetes, and with an increase in the level of Hb1Ac the amount of ApoA1 decreases. There was also significant gender difference.

With an increase in BMI, the content of ApoA1 in blood plasma decreases below normal - 0.9 g/L, and at BMI <25 kg/m^2, the amount of ApoA1 is significantly higher than the average lipoprotein level in diabetic patients.

In patients with newly diagnosed diabetes, the level of ApoA1 is significantly higher, and in patients with more than 10 years of illness, it is below average and below normal.

Treatment with biguanides, either in combination with other drugs (mainly insulin) or as monotherapy, does not significantly affect the level of ApoA1 compared to the entire group average. In patients treated with sulfonylurea, the level of ApoA1 is significantly lower than the average level for the group and the norm. A significant positive effect on the amount of ApoA1 in plasma was observed in patients treated with a combination of drugs with iSGLT2, insulin and especially DPP-4 inhibitors. However, insulin monotherapy did not significantly affect the ApoA1 content.

Possible mechanisms of apoA1 decrease in COVID-19 and diabetes are discussed.

Conclusion. Thus, the level of ApoA1 may be one of the promising markers of severe COVID-19.

Key words: apolipoprotein A1, COVID-19, diabetes mellitus, cardiovascular diseases, hypoglycemic agents.

Introduction

Apolipoprotein A1 (ApoA1), the main protein component of high-density lipoproteins (HDL), is a 243 amino acid polypeptide with an apparent molecular weight of 28 kDa. Circulating HDL particles contain single or multiple copies of ApoA1 [1]. ApoA1 is synthesized predominantly in the liver and small intestine [2]. Besides its role in HDL structure, ApoA1 is also critical for HDL functionality. ApoA1 in lipid-free form and in the nascent lipid-poor form — preβ1-HDL (consists mainly of ApoA1 and phospholipids with the molecular weight of 60–70 kDa) promotes efflux of cholesterol via the ATP-binding cassette transporter A1 (ABCA1) from macrophage foam cells and thus initiates the reverse cholesterol transport pathway from these cells, which is followed by facilitated hepatic uptake and ultimately excretion of the macrophage-derived cholesterol by the gut [1, 3]. Lipid-poor ApoA1 particles are abundant in interstitial fluids, where they can accept excess cholesterol from cholesterol-loaded cells. Recent data suggest that, by regulating cellular cholesterol homeostasis, HDL and ApoA1 can also regulate inflammatory responses in endothelial cells and other types of cells that have been activated by proinflammatory stimuli in the arterial intima [3, 4]. It has been found that increased levels of HDL-cholesterol (HDL-C) and ApoA1 in plasma are associated with a reduced risk of developing cardiovascular disease (CVD). In addition to its potential cardioprotective function, HDL and ApoA1 also have antidiabetic properties. Increases in plasma HDL and ApoA1 levels improve glycemic control in patients with type 2 diabetes mellitus by enhancing pancreatic β-cell function and improving insulin sensitivity, suggesting that interventions, which raise HDL levels, may be beneficial in diabetes-associated CVD [5, 6]. ApoA1 also stimulates glucose uptake in vivo into skeletal and cardiac muscles [7]. The ApoB/ApoA1 ratio has been found to be associated with type 2 diabetes and has been proposed as a novel biomarker for its prediction [8]. Meta-analysis also shows that decreased ApoA1 and increased ApoB levels, as well as the ApoB/A1 ratio, are risk factors for a first ischemic stroke [9].
Several clinical trials using HDL/ApoA1 infusion therapy have shown encouraging results. The use of gene transfer is an alternative way to exploit beneficial cardiovascular effects of HDL/ApoA1 in addition to HDL infusion therapy [10].

Materials and methods

The study was conducted at the Diabetology department of the Institute. The study protocol was approved by the Institute's ethics committee (protocol 2, 15.02.2021). All patients signed informed consent to conduct further diagnostic and research study.
Blood was obtained by standard venipuncture and stored in EDTA vacutainer tubes. Plasma was separated by centrifugation within 10 min after blood sampling. The samples were stored at –80 °C until use. ApoA1 was determined (n = 81) using enzyme-linked immunosorbent assay kit (Elabscience, USA). The measurement was carried out at an optical wavelength of 450 nm on the immunoenzymatic plate analyzer Stat Fax 3200 (Awareness Technology, USA).
Glycated hemoglobin was determined using one HbA1c FS kit (DiaSys Diagnostic Systems GmbH, Germany). The measurement was carried out at an optical wavelength of 660 nm.
Statistical analysis and data presentation were performed using Origin 7.0 software. The results of the study are presented as M ± m. To compare the data groups, Student's t-test was used. Values of $P \leq 0.05$ were considered significant.

Results

The blood plasma of 60 type 2 diabetes patients and 21 patients (13 women and 8 men) with diabetes and COVID-19 was used. As a control, we used the blood of healthy people (n = 7) without concomitant diseases, of representative age. The level of HbA1c in diabetic patients was 9.62 ± 0.27 %; body mass index (BMI) — 30.69 ± 1.06 kg/m2.
As seen in Fig. 1, the average level of ApoA1 in the blood of healthy people is 1.88 g/l, which is close to the upper normal range (2.02–2.25 g/l). In diabetic patients, this indicator is significantly lower — 1.21 g/l, closer to the lower limit of the norm (1.04–1.08 g/l), and in diabetic patients after recovery from COVID-19, it is lower than the norm (Fig. 1, col. 2, 3). In patients with diabetes and COVID-19, the content of ApoA1 in the

blood is approximately 0.25 g/l, which is more than 4 times lower than normal values. Interestingly, there are no differences between people with COVID-19 and diabetes, COVID-19 and CVD and patients with only COVID-19 (Fig. 1). In the blood of some individuals with COVID-19, the level of ApoA1 decreased to almost zero values — 0.09 g/l. The fact that the level of ApoA1 in the blood does not decrease in patients with COVID-19 and diabetes compared to those without diabetes indicates that COVID-19 creates significantly more powerful factors affecting the content of ApoA1, and such a decrease reaches a lower limit. It should be noted that after recovery from COVID-19, the level of ApoA1 restores, although it remains below the level in diabetic patients (Fig. 1, col. 2, 3).
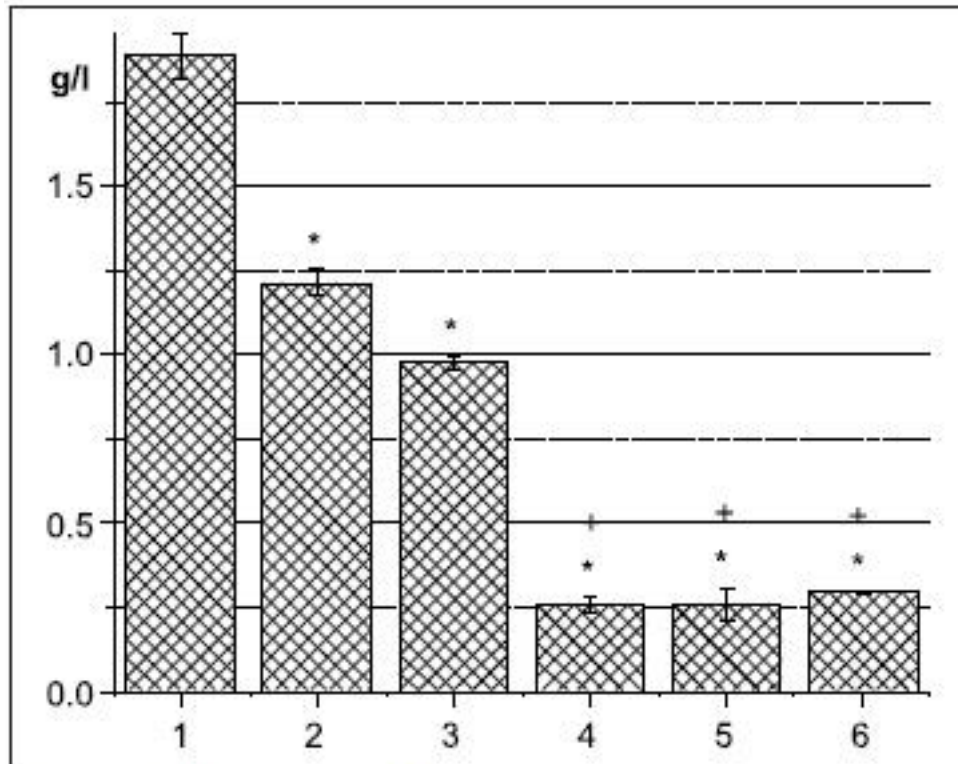

Figure 1. Plasma ApoA1 level in patients with diabetes and COVID-19: 1 — controls (n = 7); 2 — individuals with diabetes mellitus (n = 60); 3 — people with diabetes after recovery from COVID-19 (n = 8); 4 — patients with diabetes and COVID-19 (n = 16); 5 — individuals with COVID-19 (n = 5); 6 — people with COVID-19 and CVD (n = 5)

Notes: * — differences from controls are significant, $P < 0.0001$; + — differences from group 2 and 3 are significant, $P < 0.0001$; differences between groups 2 and 3 are significant, $P < 0.05$.

One of the important indicators in diabetes is the level of HbA1c. The study of the dependence of plasma ApoA1 content on the level of HbA1c, the gender of patients and the type of diabetes showed that in type 2 diabetes the amount of ApoA1 is lower than in type 1, and with an increase in the level of HbA1c the amount of ApoA1 decreases. Gender differences were also significant (Fig. 2).

Body mass index is also an important indicator in diabetes. Fig. 3 shows that with an increase in BMI, the content of ApoA1 in blood plasma decreases below normal — 0.9 g/L, and at BMI < 25 kg/m2, the amount of ApoA1 is significantly higher than the average lipoprotein level in diabetic patients (Fig. 3, col. 2, 3).

The duration of the disease also affects the content of ApoA1 in the blood plasma (Fig. 4). In patients with newly diagnosed diabetes, the level of ApoA1 is significantly higher, and in those with more than 10 years of illness, it is below average and below normal (col. 2, 3, 6).

The association of diabetes duration and glycemic control (by HbA1c level) with the risks of CVD and all-cause mortality was firmly established. Both longer diabetes duration and poorer glycemic control were associated with elevated risks of CVD and mortality.
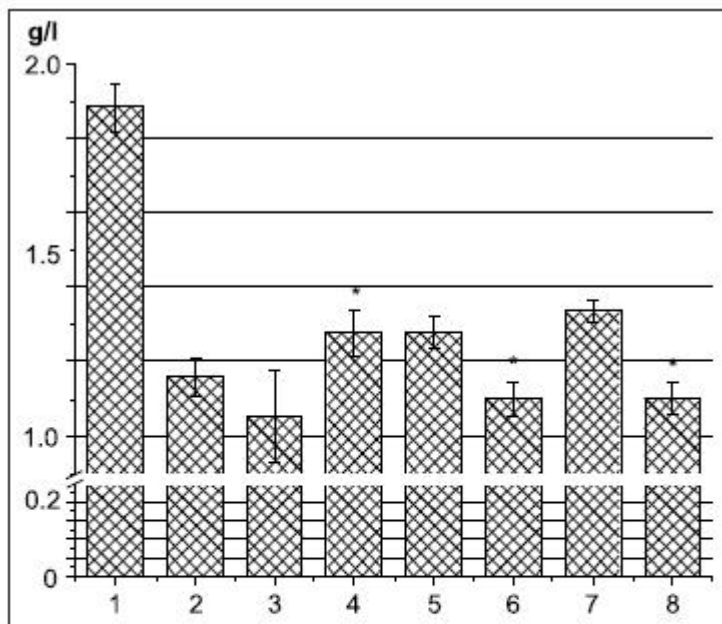
Figure 2. Effects of gender, type of diabetes and Hb1Ac level in diabetic patients on ApoA1 plasma concentration: 1 — controls; 2 — average ApoA1 level in the blood of diabetic patients; 3 — women; 4 — men; 5 — type 1 diabetes; 6 — type 2 diabetes; 7 — Hb1Ac < 8 %; 8 — Hb1Ac > 8 %

Note: * — differences between groups 3 and 4, 5 and 6, and 7 and 8 are significant, $P < 0.05$.
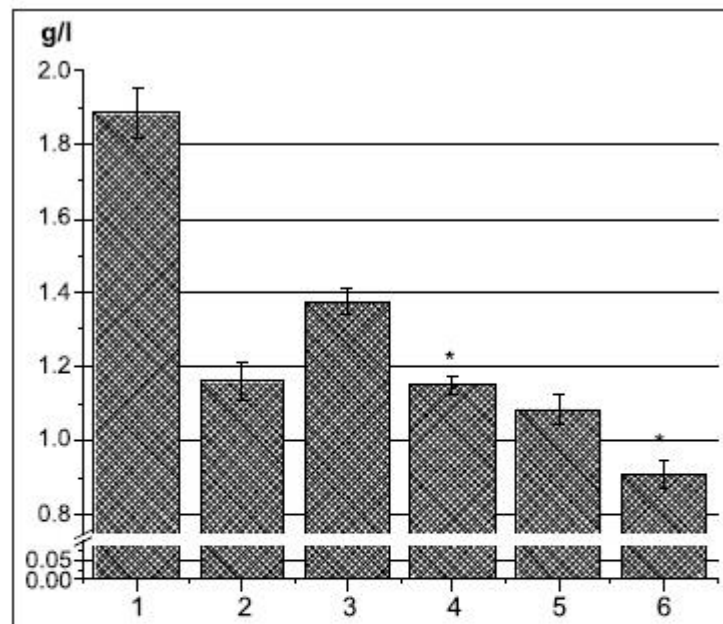

Figure 3. Effects of BMI in diabetic patients on ApoA1 plasma concentration: 1 — controls; 2 — average level of ApoA1 in the blood of diabetic patients; 3 — BMI < 25 kg/m²; 4 — BMI 25–30 kg/m², 5 — BMI > 30 kg/m², 6 — BMI > 40 kg/m²

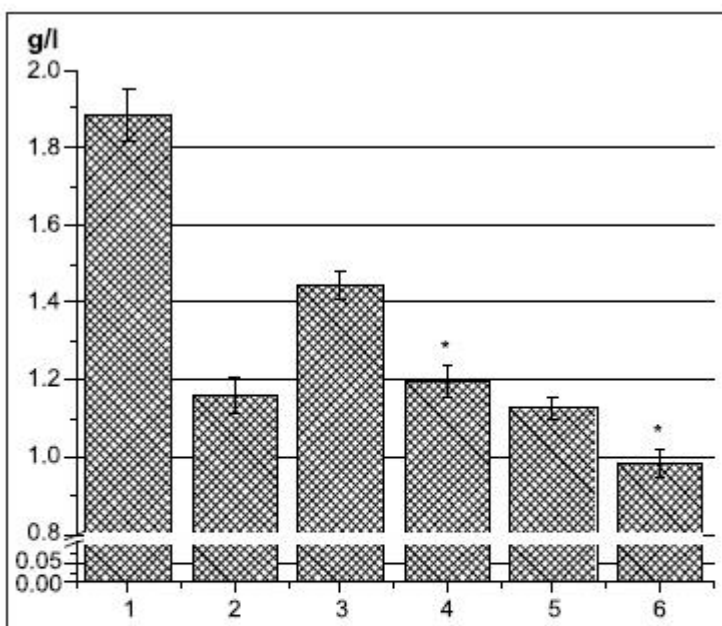Note: * — differences between this group and the previous are significant, $P < 0.05$.

Figure 4. Effects of diabetes duration on ApoA1 plasma concentration: 1 — controls; 2 — average level of ApoA1 in the blood of diabetic patients; 3 — newly diagnosed (0 years); 4 — less than 5 years; 5 — 5–10 years; 6 — over 10 years

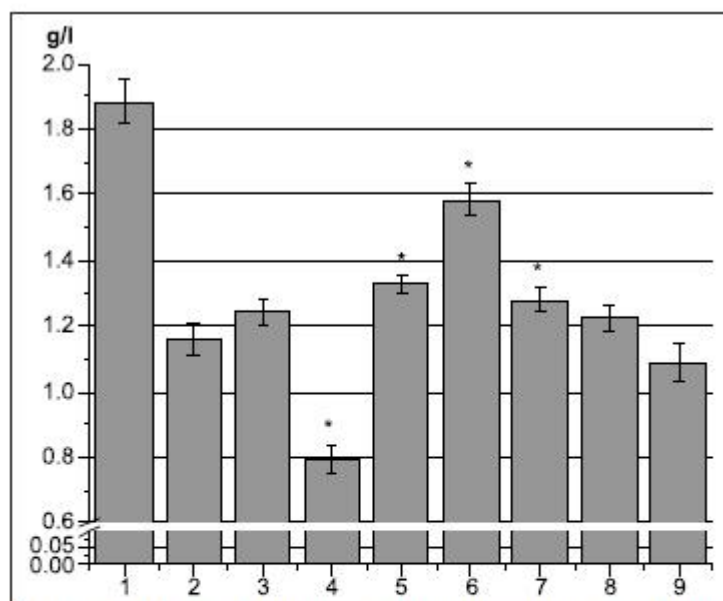Note: * — differences between this group and previous are significant, $P < 0.05$.

Figure 5. Effects of treatment of diabetic patients on ApoA1 plasma concentration: 1 — controls; 2 — average level of ApoA1 in the blood of diabetic patients (n = 60); 3 — combination with biguanides; 4 — combination with sulfonylurea; 5 — combination with iSGLT2; 6 — combination with DPP-4 inhibitors; 7 — combination with insulin; 8 — insulin monotherapy; 9 — monotherapy with biguanides

Note: * — differences between this group and average level of ApoA1 are significant, $P < 0.05$.

The ApoA1 level is influenced by the treatment method (Fig. 5). Biguanide treatment, either in combination with other drugs (mainly insulin) or as monotherapy, does not significantly affect the level of ApoA1 compared to the group average (col. 2, 3, 9). In patients treated with sulfonylurea, the level of ApoA1 is significantly lower than the average level for the entire group and the norm (col. 4). A significant positive effect on the amount of ApoA1 in plasma was observed in patients treated with a combination of drugs with sodium-glucose

cotransporter type 2 inhibitors (iSGLT2), dipeptidyl peptidase-4 (DPP-4) inhibitors and insulin (col. 5–7). However, insulin monotherapy did not significantly affect the ApoA1 content (col. 8).

Discussion

In patients with insulin resistance and type 2 diabetes, plasma lipid and lipoprotein abnormalities are common [11]. A decrease in the ApoA1 blood level of diabetic patients and an increase in the CVD risk were noted in many studies [12–14]. The association of serum HDL-C and ApoA1 levels with risk of severe SARS-CoV-2 infection is established [15]. ApoA1 was identified as the protein complex seed, and amyloid beta A4 protein, epidermal growth factor, and complement C3 were the main bottlenecks in the network. ApoA1 carries anti-inflammatory properties that could assist in the regulation of the immune response. The obtained data indicate that upregulation of C3 and downregulation of ApoA1 in urine affect respiratory rigidity and thus the severity of COVID-19 [16]. Moreover, dysregulation of amyloid beta A4 protein and ApoA1 may contribute to the possible side effects of COVID-19 on the nervous system [17].

Lipid profiles were significantly affected by COVID-19 with decreased total cholesterol, HDL-C and low-density lipoprotein (LDL) cholesterol levels and increased triglyceride concentration compared to control subjects. Plasma ApoA1 was decreased by 55 % in patients versus controls [18]. COVID-19-induced hypolipidemia positively correlated with the severity of disease [19]. Decreased ApoA1 levels in COVID-19 patients suggest decreased synthesis by the liver and/or its replacement by serum amyloid A in HDL [18]. A decrease in ApoA1 was also associated with the pathogenesis of chronic hypersensitivity pneumonitis in terms of pulmonary fibrosis and mast cell chymase attenuated the protective effect of ApoA1 against pulmonary fibrosis. These results suggest that chymase produced by mast cells may play an important role in the degradation of ApoA1 [2, 20]. In addition, carboxypeptidase A and matrix metalloproteinases 3 and 14 can be involved in the degradation of ApoA1 [20, 21]. Inflammatory cytokines such as tumor necrosis factor and interleukin 1β, which are secreted in large quantities during COVID-19 infection, suppress the production of ApoA1 from hepatocytes and increase the expression of serum amyloid A, which becomes the major protein component of HDL in this context [10]. Finally, the regulation of ApoA1 expression can occur at the transcriptional level [22].

HbA1c was found to have significant positive correlation with total cholesterol, LDL-C, and triglyceride and significant negative correlation with HDL-C and HDL/LDL ratio [23]. Subjects with HbA1c-defined prediabetes and type 2 diabetes, respectively, are characterized by abnormalities in lipid profile — lower ApoA1 and HDL cholesterol levels [24].

It was shown that larger BMI, higher glucose levels, and lower content of ApoA1 are significantly and independently associated with newly diagnosed type 2 diabetes. Lower ApoA1 improved the risk prediction of new newly diagnosed 2 diabetes when it was added to the existing risk models [25]. Also, obesity, especially central obesity, contributes more to increasing ApoB/ApoA1 ratio than increased blood pressure, and other indices in women with polycystic ovary syndrome aged 20–38 years [26]. Obesity is associated with a state of chronic inflammation and increased cardiometabolic disease risk. All biomarkers were significantly associated with BMI: ApoA1, HDL-C, and 25(OH)D were inversely associated with BMI [27].

Clinicians should consider not only glycemic control but also diabetes duration in CVD risk assessments for participants with diabetes [28].

A significant decrease in the level of ApoA1 compared to its average content in diabetic patients after combined treatment with sulfonylurea is of particular interest. Some studies suggest that sulfonylureas may affect cardiac function and also may be associated with poorer outcomes after myocardial infarction [29]. Increased mortality from cardiovascular disease in diabetic patients taking tolbutamide was reported in the past decades. In the Mayo Clinic, in 185 consecutive diabetic patients undergoing percutaneous coronary intervention after myocardial infarction, the odds ratio for death was 2.77 for those treated with a sulfonylurea at the time of the myocardial infarction [29, 30]. Besides, high dose (500 μM) of glibenclamide inhibited ABCA1 function and ApoA1-mediated cholesterol efflux, and attenuated ABCA1 expression [31] that can lead to the accumulation of cholesterol in macrophages of atherosclerotic plaques. A decrease in the level of ApoA1 may be a reflection of the negative processes taking place during the treatment with sulfonylurea.

On the contrary, combination of drugs with iSGLT2 and DPP-4 inhibitors caused a small but significant increase in the level of ApoA1, which is consistent with their positive effect on cardiovascular function in diabetes [32, 33]. Moreover, glucagon-like peptide-1 receptor agonist, DPP-4 inhibitors and iSGLT2 can improve diabetic dyslipidemia [34].

Biguanide treatment, either in combination with other drugs (mainly insulin) or as monotherapy, does not significantly affect the level of ApoA1. The combined treatment with insulin and other drugs had a small positive effect on the level of ApoA1. It is known that hyperinsulinemia is an atherogenic factor [35], but

treatment with insulin in combination with DPP-4 and iSGLT2 may lead to an increase in the plasma amount of ApoA1. The positive effect of metformin and especially the combination of metformin and insulin on the cardiovascular system may be explained by a decrease in endothelin-1 and NT-proBNP concentrations and by an increase in glucagon-like peptide-1 [36, 37].

Conclusions

ApoA1 level in the blood of patients with diabetes and especially with COVID-19 was significantly lower than in the blood of healthy people. The content of ApoA1 may be one of the promising markers of severe COVID-19.

The study of the dependence of the ApoA1 plasma content on the Hb1Ac level, the patients' gender and the type of diabetes showed that in blood of individuals with type 2 diabetes, the ApoA1 amount is lower than in those with type 1 diabetes, and with an increase in the level of Hb1Ac the amount of ApoA1 decreases. There was also significant gender difference.

With an increase in BMI, the ApoA1 content in blood plasma decreases below normal — 0.9 g/l, and at BMI < 25 kg/m2, the amount of ApoA1 is significantly higher than the average lipoprotein level in diabetic patients.

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Biguanide treatment, either in combination with other drugs (mainly insulin) or as monotherapy, does not significantly affect the level of ApoA1 compared to the entire group average. In patients treated with sulfonylurea, the level of ApoA1 is significantly lower than the average level for the group and the norm. A significant positive effect on the amount of ApoA1 in plasma was observed in patients treated with a combination of drugs with iSGLT2, insulin and especially DPP-4 inhibitors. However, insulin monotherapy did not significantly affect the ApoA1 content.

Possible mechanisms of ApoA1 decrease in COVID-19 and diabetes are discussed.

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