

Fetuin-A as a biomarker of the hepatoprotective effect of gliflozin in patients with type 2 diabetes and nonalcoholic steatohepatitis

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Abstract. Non-alcoholic steatohepatitis (NASH) in patients with type 2 diabetes (T2D) remains one of the leading medical and social problems of a modern time due to the increased risk of developing steatogenic liver cirrhosis and macrovascular complications. Metabolic dysfunction-associated steatotic liver disease worsens the course of T2D and forms a continuum of pathogenetic disorders. Modern therapeutic strategies require the introduction of biomarkers that reflect the effectiveness of treatment and help to evaluate alternative mechanisms of pharmacological effect of hypoglycemic drugs. **The aim** is to determine the level of fetuin-A as a marker of hepatoprotective efficacy of a 12-week course of therapy with sodium-dependent glucose cotransporter 2 inhibitors (SGLT2i) in individuals with T2D and NASH. **Material and methods.** The study included 48 patients with T2D and NASH, who were divided into four groups according to their therapeutic strategy: Group I (n=12) received basic drug therapy (BDT): metformin 2000 mg/day, α -lipoic acid 600 mg/day, rosuvastatin 10 mg/day; Group II (n=12) – BDT in combination with insulin therapy; Group III (n=12) received BDT in combination with 10 mg/day dapagliflozin (DAPA); Group IV (n=12) received BDT in combination with 10-25 mg/day empagliflozin (EMPA). The study lasted 12 weeks. **Results.** After 12 weeks of treatment, the most pronounced hepatoprotective effect was observed in patients of groups III and IV who received gliflozins as part of BDT. Mediation analysis showed that when insulin therapy was used, the reduction in fetuin-A levels was almost entirely due to improved glycemic control through glycated hemoglobin (HbA1c) (ACME=-0.10; 95% CI -0.22; -0.01), while the direct hepatocentric effect was minimal. SGLT2i in groups III and IV of the study enhanced the reduction in fetuin-A content, both indirectly through HbA1c (ACME = -0.23 and -0.20) and directly (ADE -0.32 and -0.30; both $p < 0.01$), with about 40% of the effect explained by the glycemic mechanism and the rest by direct hepatoprotective properties. **Conclusions.** Assessment of fetuin-A level as an early biomarker of the hepatoprotective effect of gliflozins allows to improve personalized NASH therapy in patients with T2D. Timely prescription of SGLT2i (DAPA 10 mg/day or EMPA 10-25 mg/day) as part of BDT is an effective, pathogenetically justified treatment algorithm with pronounced hepatoprotective properties.

Keywords: type 2 diabetes, insulin resistance, non-alcoholic steatohepatitis, fetuin-A, sodium-glucose cotransporter 2 inhibitors, dapagliflozin, empagliflozin.

Metabolic diseases are considered a non-communicable pandemic of our time, among which diabetes mellitus and metabolic-associated steatohepatitis (MASH) cause the greatest medical and social burden [1-4]. In patients with T2D, NASH occurs much more often than in the general population and is associated with a more severe course [5, 6], which necessitates the search for new therapeutic strategies and reliable markers to monitor their effectiveness. An early prognostic marker of metabolic and inflammatory disorders is fetuin-A, a glycoprotein of hepatocyte origin. Increased levels of this hepatokine are associated with insulin resistance (IR), obesity, systemic inflammation, progression of NASH, and a high risk of cardiovascular complications. [7-11]. The study of the dynamics of fetuin-A allows us to consider it as an early laboratory marker for assessing the severity of liver steatosis and fibrosis, as well as in patients with comorbid metabolic disorders. Currently, there are no specifically approved drugs for the treatment of NASH in patients with T2D, which emphasizes the importance of studying the hepatocentric and pleiotropic effects of hypoglycemic agents. SGLT2i (gliflozins) attract special attention, which, in addition to improving glycemic control, demonstrate hepatoprotective properties: they reduce signs of hepatic IR, steatosis, and liver inflammation, prevent the progression of fibrosis, and have a positive effect on metabolic parameters [12-16]. At the same time, the available data on the impact of gliflozins (DAPA and EMPA) on the level of fetuin-A remains insufficient, which underscores the relevance of the study and opens up prospects for investigating their hepatoprotective properties.

The lack of uniform international recommendations for drug therapy of NASH emphasizes the need to improve patient-centered treatment algorithms for people with T2D, aiming to reduce the risk of progression of the metabolic continuum and improve clinical prognosis.

Therefore, our study aimed to assess the level and dynamics of fetuin – A as a marker of hepatoprotective efficacy of a 12-week course of therapy SGLT2i in people with T2D and NASH.

Material and methods

After obtaining written informed consent, 48 patients with T2D and NASH were included in the study (mean age – 53.00 ± 9.54 years; metabolic age – 69.65 ± 7.45 years; duration of T2D – $8.10 \pm$

± 4.45 years), among whom 75% were men. Patients underwent a 12-week course of treatment on the basis of the Endocrinological and Outpatient Departments of the Communal Non-commercial Enterprise «Regional Clinical Hospital of Ivano-Frankivsk Regional Council».

All stages of the study were performed in accordance with the principles of the Helsinki Declaration and current national and international regulatory legal acts in the field of bioethics and were approved by the Ethics Committee of Ivano-Frankivsk National Medical University (protocol No. 139/23 dated 11/16/2023).

Basic clinical and laboratory characteristics of patients included anthropometric indicators, carbohydrate and lipid profile, level of fetuin-A, and instrumental parameters of NASH are presented in **Table 1**.

Inclusion criteria:

- patients aged 18 to 80 years;
- confirmed diagnosis of T2D;
- confirmed diagnosis of NASH;
- HbA_{1c} level $\leq 11.0\%$;
- stable monotherapy with metformin at a daily dose of 2000 mg for at least three months prior to inclusion.

Exclusion criteria:

- age over 80 years;
- type 1 diabetes;
- ketoacidosis of any origin;
- alcohol consumption ≥ 14 servings/week in men and ≥ 7 servings/week in women;
- acute viral hepatitis;
- alternative forms of liver diseases: chronic viral hepatitis, drug-induced hepatitis, primary biliary cirrhosis, autoimmune hepatitis, hepatocellular carcinoma, idiopathic hemochromatosis, Konovalov-Wilson disease;
- acute cerebrovascular disorders;
- hypertrophic, dilated and restrictive cardiomyopathy;
- oncological diseases;
- terminal stages of chronic kidney disease and heart failure;
- hematological diseases;
- pregnancy or lactation;
- existing contraindications to the use of the study drugs
- incapacity or limited capacity, alcohol or drug addiction;
- history of bariatric surgery.

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Table 1. Basic clinical and laboratory characteristics of the studied patients with T2D and NASH based on gender

Parameters	Enrolled patients			P value
	All patients (n=48)	Male (n=36)	Female (n=12)	
Demographic data				
Age, years	53.00±9.54	52.36±9.16	54.92±10.77	0.471
Metabolic age, years	69.65±7.45	69.44±7.16	70.25±8.59	0.773
Duration of type 2 DM, years	8.10±4.45	7.96±4.05	8.50±5.66	0.765
Anthropometric data				
BMI, kg/m ²	33.57±3.74	32.51±3.17	36.78±3.59	0.002
VAI	3.76±1.83	3.34±1.58	5.02±2.03	0.019
WC, cm	111.17±5.92	111.44±6.19	110.33±5.18	0.547
TBF, %	39.15±7.30	36.51±5.30	47.07±6.86	0.000
VBF, units	36.26±6.92	34.12±5.54	42.66±6.87	0.001
Body mass profile:				
Obesity	8 (16.7%)	8 (22.2%)	0 (0.0%)	0.180
Class I	25 (52.1%)	21 (58.3%)	4 (33.3%)	0.243
Class II	13 (27.1%)	7 (19.4%)	6 (50.0%)	0.091
Class III	2 (4.2%)	0 (0.0%)	2 (16.7%)	0.095
Biochemistry				
HbA _{1c} , %	9.27±1.39	9.22±1.39	9.40±1.45	0.705
FSG, mmol/L	9.29±2.14	8.88±2.13	10.50±1.72	0.014
HOMA-IR	3.87±1.16	3.70±1.03	4.39±1.40	0.140
FetA, ng/mL	19.93±2.90	19.98±3.08	19.77±2.40	0.814
Lipid profile				
FPG, mmol/L	6.00±0.84	5.93±0.81	6.20±0.95	0.387
TG mmol/L	2.43±0.74	2.38±0.78	2.58±0.64	0.373
HDL-C, mmol/L	1.24±0.19	1.24±0.20	1.24±0.19	0.959
LDL-C, mmol/L	3.67±0.87	3.70±0.78	3.60±1.13	0.794
VLDL-C, mmol/L	1.35±0.91	1.25±0.86	1.65±1.00	0.226
AC	3.93±0.91	3.87±0.90	4.08±0.95	0.509
Laboratory and instrumental parameters of NASH				
De Ritis coefficient (ALT/AST)	1.01±0.13	1.04±0.13	0.92±0.11	0.005
FIB-4 index	2.47±0.55	2.39±0.52	2.69±0.61	0.145
APRI	1.13±0.28	1.12±0.28	1.16±0.31	0.657
HEPAmet	0.50±0.16	0.47±0.13	0.61±0.20	0.037
Stage of liver fibrosis according to METAVIR scale based on SWE, kPa				
F2 (7.0-9.5 kPa)	5 (10.4%)	4 (11.1%)	1 (8.3%)	1.000
F3 (9.5-12.5 kPa)	43 (89.6%)	32 (88.9%)	11 (91.7%)	1.000

Note. AC – atherogenicity coefficient; ALT – alanine aminotransferase; AST – aspartate aminotransferase; APRI – AST to platelet ratio index; BMI – body mass index; FIB-4 index – liver fibrosis index-4; FSG – fasting serum glucose; HDL-C – high-density lipoprotein cholesterol; HEPAmet – validated liver fibrosis severity assessment system; HOMA-IR – homeostatic model of insulin resistance; LDL-C – low-density lipoprotein cholesterol; METAVIR – liver stiffness assessment scale according to shear wave elastography results; SWE – shear wave elastography; TBF – total fat content; TCH – total cholesterol; TG – triglycerides; VAI – visceral adiposity index; VBF – visceral fat content; VLDL-C – very low-density lipoprotein cholesterol; WC – waist circumference.

Diagnostic criteria. The diagnosis of T2D was established if one of the following criteria was present: HbA_{1c} level $\geq 6.5\%$ (≥ 48 mmol/mol); two consecutive fasting capillary blood glucose (FBG) determinations ≥ 7.0 mmol/L with an interval of more than half a year; confirmed diagnosis of T2D

in the medical records in combination with the fact of constant intake of hypoglycemic drugs [17].

The diagnosis of NASH was established in accordance with the provisions of the unified clinical protocol approved by the Order of the Ministry of Health of Ukraine No. 826 dated 06.11.2014, and

guideline 01114 «Non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH)» (last update – 12.04.2015). Additionally, international recommendations for the diagnosis and treatment of NAFLD were taken into account, in particular the guidelines of the American Association for the Study of Liver Diseases (AASLD, 2023), the European Association for the Study of Liver Diseases (EASL), the European Association for the Study of Diabetes (EASD) and the European Association for the Study of Obesity (EASO, 2023) [18].

To achieve study goal four study groups were formed based on therapeutic strategy: Group I (n=12) received basic drug therapy (BMT): metformin 2000 mg/day, α -lipoic acid 600 mg/day, rosuvastatin 10 mg/day; Group II (n=12) – BMT in combination with insulin therapy; Group III (n=12) – BMT in combination with 10 mg/day DAPA; Group IV (n=12) – BMT together with the use of 10-25 mg/day EMPA.

The effectiveness of the 12-week course of therapy was assessed by the dynamics of clinical, biochemical and instrumental parameters with subsequent determination of specific indicators of non-invasive indices of liver steatosis and fibrosis: hepatic steatosis index (HSI), fibrosis index FIB-4 (Fibrosis-4), APRI (aspartate aminotransferase to platelet ratio index), validated liver fibrosis severity assessment system [19-21].

According to standard methods, patients underwent a clinical examination with determination of anthropometric indicators (height, body weight, waist and hip circumference), assessment of body composition (total fat content, visceral fat (VF), fat-free mass (FFM), bone and muscle mass), as well as calculation of visceral adiposity index. The body composition monitor Tanita BC-601 (Japan), which works by the bioimpedance measurement method with additional determination of metabolic age, was used for the analysis.

Carbohydrate metabolism indicators (HbA_{1c}, fasting capillary blood glucose (FCG) level, insulin concentration in blood plasma) and lipid spectrum parameters were studied: total cholesterol, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, very-low-density lipoprotein cholesterol, as well as the atherogenic index plasma (AIP).

In this study we used enzyme-linked immunosorbent assay (ELISA) to determine the level of

fetuin-A (alpha-2-HS glycoprotein (AHSG)) in blood serum, according to the instructions attached to the MyBioSource, Inc. (San Diego, USA) reagent kit.

In addition, shear wave elastography of the liver was performed on an expert-class LOGIQ S8 ultrasound scanner (General Electric, USA). The assessment of liver tissue stiffness was interpreted according to the liver stiffness assessment scale according to shear wave elastography results (METAVIR scale) (kPa): 2.5-6.0 kPa – no fibrosis (F0); 6.0-7.0 kPa – mild fibrosis (F1); 7.0-9.5 kPa – moderate fibrosis (F2); 9.5-12.5 kPa – severe fibrosis (F3); ≥ 12.5 kPa – cirrhosis (F4) [22].

Statistical data analysis was performed in Python 3.11 using Scipy.stats, Numpy, Statsmodels libraries. Normality of distribution was checked by the Shapiro-Wilk test; in case of deviation ($p < 0.05$), nonparametric tests (Mann-Whitney, Wilcoxon, Kruskal-Wallis) were used. Qualitative variables were assessed using the χ^2 test or Fisher's exact test. Logistic models, according to the Baron-Kenny method, were used for regression and mediation analysis. Statistical significance was accepted at the $p < 0.05$ level.

Results and discussion

At the initial stage of the study, a regression-correlation analysis of the relationship between the level of fetuin-A and clinical, biochemical and instrumental parameters of NASH in patients with T2D was performed. A statistically significant positive correlation was established between the content of fetuin-A with the level of HbA_{1c} ($R=0.568$; $p < 0.001$), indicators of hepatic transaminases: aspartate aminotransferase ($R=0.368$; $p=0.010$) and alanine aminotransferase ($R=0.369$; $p=0.010$), as well as with indicators of liver stiffness according to the ZHEG data ($R=0.396$; $p=0.005$) and the METAVIR scale ($R=0.308$; $p=0.033$). For other anthropometric, laboratory and instrumental characteristics of NASH, no significant correlations were found ($p > 0.05$) (**Table 2**).

Experimental and clinical studies confirm a close relationship between NASH and the level of fetuin-A [9, 10, 23]. In particular, a recently published retrospective study demonstrated that in patients with NASH, an increase in the concentration of fetuin-A in the blood serum reflects an inflammatory response or cellular stress, causing excessive release

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Table 2. Regression-correlation analysis of the relationship between fetuin-A and clinical and biochemical parameters in patients with T2D and NASH at baseline (n=48)

Parameters	R	P value
Age, years	-0.111	0.452
Metabolic age, years	-0.246	0.092
Type 2 DM, years	0.023	0.879
Weight, kg	-0.147	0.320
BMI, kg/m ²	-0.056	0.706
IBO	-0.127	0.391
WC, cm	-0.130	0.380
TC, cm	-0.077	0.603
BFP, %	0.060	0.687
VFP, units	-0.011	0.942
HbA _{1c} , %	0.568	<0.001*
FSG, mmol/L	-0.062	0.677
HOMA-IR	-0.036	0.809
TCH, mmol/L	0.196	0.181
TG, mmol/L	-0.087	0.558
LDL-C, mmol/L	0.230	0.115
VLDL-C, mmol/L	0.115	0.436
HDL-C, mmol/L	0.029	0.847
AIP	-0.060	0.686
AST, IU/L	0.368	0.010*
ALT, IU/L	0.369	0.010*
FIB-4	-0.039	0.794
APRI	0.183	0.213
HSI	-0.010	0.947
SWE of liver, kPa	0.396	0.005*
METAVIR scale	0.308	0.033*

Note. See table 1; * $p < 0.05$; AIP - atherogenic plasma index; TC - thigh circumference.

of this glycoprotein by damaged hepatocytes [24]. It should be emphasized that, given the literature data [7, 11] and the results of multivariate regression analysis (**Table 3, Figure**), it is justified to

Table 3. Multivariate regression analysis of the influence of clinical and biochemical parameters on fetuin-A in patients with T2D and NASH (n=48)

Parameters	β	95% CI	P value
HbA _{1c} , %	0.458	0.261-0.655	0.000
AST, IU/l	0.609	0.153-1.066	0.010
ALT, IU/l	0.481	0.121-0.840	0.010
SWE of liver, kPa	0.247	0.077-0.417	0.005
METAVIR scale	0.331	0.028-0.635	0.033

consider fetuin-A a potential predictor of the development and progression of NASH in patients with T2D.

At the present stage, the dynamics of fetuin-A level in response to hypoglycemic therapy are actively studied.

Table 4 shows changes in fetuin-A level in the studied patients. At the beginning of the observation, the average values of this indicator were similar in all groups: BMT – 20.10 [17.90-23.02] ng/mL, addition to BMT: insulin therapy – 19.65 [18.38-20.75] ng/mL; EMPA – 20.45 [18.57-21.35] ng/mL and DAPA – 19.85 [18.43-21.38] ng/mL, no statistically significant differences between them were found ($p=0.96$).

To assess the effectiveness of therapy, after 12 weeks of treatment, fetuin-A level in group I of the studied individuals remained practically unchanged (19.55 [17.58-22.62] ng/mL, Δ -1.83%; $p=0.360$). The addition of insulin therapy was accompanied by a tendency to decrease (18.30 [17.08-19.35] ng/mL, Δ -6.85%; $p=0.070$), which did not reach statistical significance. In contrast, the use of SGLT2i had a pronounced effect: in group III patients receiving EMPA, fetuin-A level decreased to

Table 4. Serum fetuin-A levels in study groups (median, 25-75 percentile)

Fetuin-A serum levels	Study groups				p-value
	I (n=12)	II (n=12)	III (n=12)	IV (n=12)	
Before treatment	20.10 [17.90-23.02]	19.65 [18.38-20.75]	20.45 [18.57-21.35]	19.85 [18.43-21.38]	0.96
12 weeks of treatment	19.55 [17.58-22.62]	18.30 [17.08-19.35]	14.55 [12.78-15.22]	14.15 [13.07-15.00]	<0.001
Δ %;	-1.83%;	-6.85%;	-29.94%;	-29.47%;	-
p before vs after treatment	0.360	0.070	0.002	0.002	
Post-hoc comparison after treatment					
I vs II	I vs III	I vs IV	II vs III	II vs IV	III vs IV
>0.05	0.006	0.004	< 0.001	< 0.001	>0.05

Note. 4% – percentage change in fetuin-A levels after treatment.

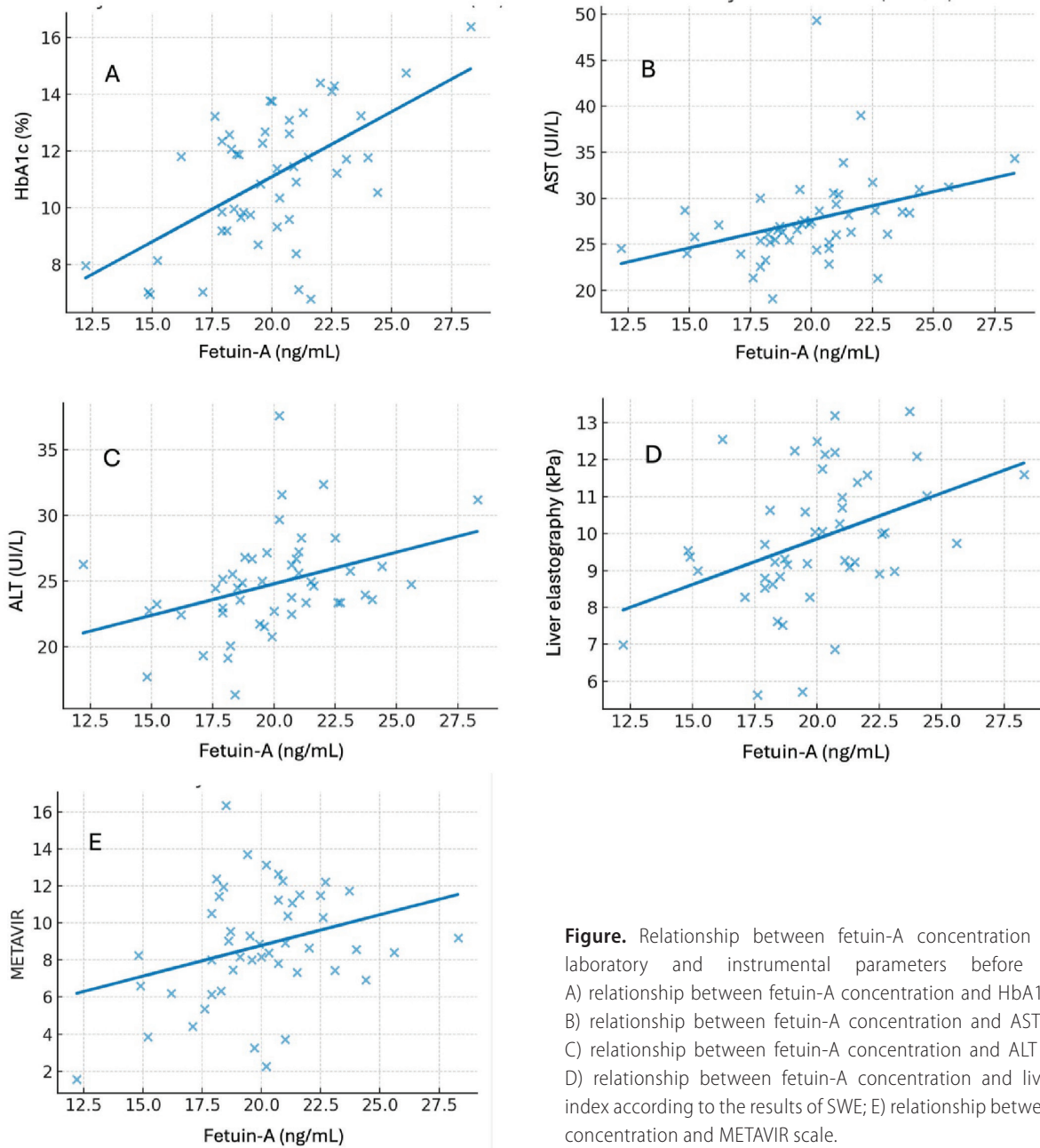


Figure. Relationship between fetuin-A concentration and some laboratory and instrumental parameters before treatment: A) relationship between fetuin-A concentration and HbA1C, level, %; B) relationship between fetuin-A concentration and AST level, IU/l; C) relationship between fetuin-A concentration and ALT level, IU/L; D) relationship between fetuin-A concentration and liver stiffness index according to the results of SWE; E) relationship between fetuin-A concentration and METAVIR scale.

14.55 [12.78-15.22] ng/mL (Δ -29.94%; $p=0.002$), and in group IV – to 14.15 [13.07-15.00] ng/mL (Δ -29.47%; $p=0.002$). The overall intergroup difference after treatment was highly significant ($p<0.001$).

No statistically significant differences were found between BMT and in combination with insulin therapy ($p>0.05$). At the same time, both EMPA and DAPA demonstrated a significantly better effect compared to BMT ($p=0.006$ and $p=0.004$, respectively) and insulin therapy (both $p<0.001$). These two SGLT2i didn't differ significantly

between themselves ($p>0.05$). The obtained data are consistent with the results of most scientific observations. The positive effect of biguanides on reducing the concentration of this hepatokine in patients with fatty liver disease has been proven [25]. At the same time, no statistically significant differences in fetuin-A level between individuals with T2D receiving oral hypoglycemic therapy and those being on insulin therapy were found [26]. The results of modern studies indicate the promising effect of SGLT2i, which contribute to the improvement of lipid metabolism and the reduction in

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Table 5. Efficacy of treatment algorithms studied in patients with T2D and NASH

Study groups	a	b	ACME	95% CI ACME	ADE	Total effect	Mediation proportion
II vs I	-0.35	0.28	-0.10	-0.22; -0.01	-0.15	-0.25	0.40
III vs I	-0.90	0.26	-0.23	-0.42; -0.07	-0.32	-0.55	0.42
IV vs I	-0.85	0.24	-0.20	-0.38; -0.05	-0.30	-0.50	0.40
III vs II	-0.55	0.23	-0.13	-0.28; 0.01	-0.19	-0.32	0.41
IV vs II	-0.50	0.22	-0.11	-0.25; 0.00	-0.17	-0.28	0.39
III vs IV	0.05	0.21	0.01	-0.08; 0.10	0.02	0.03	-

Note. a – coefficient a of the treatment effect on $\Delta\text{HbA}_1\text{C}$; ACME - average causal mediation effect; ADE - average direct effect; b - coefficient b of the treatment-adjusted $\Delta\text{HbA}_1\text{C}$ effect on $\Delta\text{Fetuin-A}$.

fetuin-A levels, which has been confirmed both in experimental models and in clinical trials [13, 15, 27, 28].

To assess the indirect effect of therapy on fetuin-A levels through changes in HbA_1C , the Baron–Kenny approach with regression models was used. The indirect effect (ACME, average causal mediation effect) was calculated as the product of the coefficients a (treatment effect on $\Delta\text{HbA}_1\text{C}$) and b (treatment-adjusted effect of $\Delta\text{HbA}_1\text{C}$ on $\Delta\text{Fetuin-A}$). Due to the asymmetric distribution of the product of the coefficients, the reliability of ACME was assessed by the bootstrapping method (5000 resamples). The indirect effect was considered statistically significant if the 95% confidence interval did not include zero. Direct (ADE, average direct effect) and total (Total) effects were determined using t-tests with robust standard errors (HC3). For interpretation the mediation proportion (ACME/Total) was also presented.

The results of the mediation analysis indicate that the decrease in fetuin-A concentration under the influence of the proposed treatment algorithms is mainly associated with improved glycemic control, however, the role of this mechanism differed depending on the choice of hypoglycemic drugs.

In comparing the BMT treatment complex and the addition of insulin therapy (group II) with the control group (group I), a statistically significant mediated glucose-centric effect through HbA_1c was established (ACME=-0.10; 95% CI: -0.22 – -0.01), while the direct effect, probably related to hepatoprotective properties (ADE=-0.15; p=0.04), was relatively weak. The obtained data indicate that the effect of insulin therapy on reducing fetuin-A level is mainly due to improved glycemic control.

The use of SGLT2i in groups III (DAPA) and IV (EMPA) was accompanied by a pronounced decrease in fetuin-A level both indirectly through HbA_1c (ACME for group III vs group I = -0.23; 95% CI: -0.42 – -0.07; for group IV vs group I = -0.20; 95% CI: -0.38 – -0.05), and directly (ADE= -0.32 and -0.30, respectively; both p < 0.01). The overall effect of gliflosins was -0.55 and -0.50, of which almost 40% was due to an improvement in the glycemic profile, while approximately 60% was due to hepatocentric mechanisms, probably related to the regulation of hepatic steatosis, reduction of inflammation and insulin resistance.

Direct comparison of treatment algorithms with the addition of SGLT2i to BMT and BMT in combination with insulin therapy (study groups: III vs II and IV vs II) revealed both indirect (ACME= -0.13; -0.11) and direct hepatoprotective effects (ADE= -0.19; -0.17). In the available sample, the confidence intervals partially included zero, indicating a trend towards the superiority of gliflosins over insulin therapy without statistical significance.

Comparison of BMT combined with DAPA (group III) and EMPA (group IV) didn't demonstrate significant differences in direct (ADE=0.02; p=0.72) or indirect metabolic effects (ACME=0.01; 95% CI: -0.08, 0.10) on reducing fetuin-A levels, confirming their equivalence (**Table 5**).

Thus, the results of the mediation analysis confirmed that insulin therapy reduces fetuin-A level mainly due to improved HbA_1c , while gliflosins implement a combined effect: about 40% of the effect is due to glucose-centric mechanisms, and a larger proportion (~60%) - to the hepatoprotective effect. No statistically significant differences were observed between DAPA and EMPA, which confirms the presence of a class effect.

Conclusions

Evaluation of fetuin-A level as an early biomarker allows predicting the hepatoprotective effect of gliflozins and optimizing personalized nonalcoholic steatohepatitis therapy in patients with type 2 diabetes. Timely administration of inhibitors of the sodium-glucose cotransporter type 2 (dapagliflozin 10 mg/day or empagliflozin 10-25 mg/day) as part of basic drug therapy is an effective and pathogenetically justified treatment algorithm with pronounced hepatoprotective properties.

Future research perspective will be focused on studying the multifaceted metabolic properties of gliflozins and confirming their class-specific hepatocentric effect, while simultaneously assessing the dynamics of fetuin-A as an early biomarker of the effectiveness of hypoglycemic therapy. Such studies require large-scale clinical and experimental work and open up new opportunities for optimizing NASH treatment algorithms in patients with and without T2D.

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List of abbreviations

DAPA – dapagliflozin

EMPA – empagliflozin

HbA_{1c} – glycated hemoglobin

METAVIR – liver stiffness assessment scale according to shear wave elastography results

NASH – nonalcoholic steatohepatitis

SGLT2i – inhibitors of the sodium-glucose cotransporter type 2

T2D – type 2 diabetes

Фетуїн-А як біомаркер гепатопротекторної дії гліфлозинів у пацієнтів із цукровим діабетом 2-го типу та неалкогольним стеатогепатитом

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Резюме. Неалкогольний стеатогепатит (НАСГ) у пацієнтів із цукровим діабетом 2-го типу (ЦД2) залишається однією з провідних медико-соціальних проблем сучасності через підвищення ризику розвитку стеатогенного цирозу печінки та макроваскулярних ускладнень. Метаболічно-асоційована стеатотична хвороба печінки погіршує перебіг ЦД2 та формує континуум патогенетичних порушень. Сучасні терапевтичні стратегії потребують впровадження біомаркерів, які відображають ефективність лікування та допомагають оцінити альтернативні механізми фармакологічної дії цукрознижувальних лікарських засобів. **Мета** – оцінити рівень та динаміку фетуїну-А як маркера гепатопротекторної ефективності 12-тижневого курсу терапії інгібіторами натрійзалежного котранспортера глюкози 2-го типу (іНЗКТГ-2) в осіб із ЦД2 та НАСГ. **Матеріал і методи.** У дослідження було включено 48 пацієнтів із ЦД2 та НАСГ, які за терапевтичною стратегією розподілені на чотири групи: група I (n=12) отримувала базову медикamentозну терапію (БМТ): метформін 2000 мг/добу, α-ліпоєву кислоту 600 мг/добу, розувастатин 10 мг/добу; група II (n=12) – БМТ у по-

єднанні з інсулінотерапією; група III (n=12) – БМТ у комбінації з 10 мг/добу дапагліфлозином (ДАПА); група IV (n=12) – БМТ разом із застосуванням 10-25 мг/добу емпагліфлозину (ЕМПА). Тривалість дослідження становила 12 тижнів. **Результати.** Через 12 тижнів лікування найвираженіший гепатопротекторний ефект спостерігався в пацієнтів груп III та IV, які отримували гліфлозини у складі БМТ. Медіаційний аналіз продемонстрував, що при застосуванні інсулінотерапії виявлено зниження рівня фетуїну-А, майже в повному обсязі зумовлене покращенням глікемічного контролю через HbA_{1c} (АСМЕ=-0,10; 95% ДІ -0,22; -0,01), тоді як прямий гепатоцентричний ефект був мінімальним. іНЗКТГ-2 у групах III та IV підсилювали зниження вмісту фетуїну-А, як опосередковано через HbA_{1c} (АСМЕ = -0,23 та -0,20), так і прямим шляхом (АДЕ = -0,32 та -0,30; обидва p<0,01), при цьому близько 40% ефекту пояснювалося глікемічним механізмом, а решта – безпосередніми гепатопротекторними властивостями. **Висновки.** Оцінка рівня фетуїну-А як раннього біомаркера гепатопротекторного ефекту гліфлозинів дозволяє вдосконалити персоналізовану терапію НАСГ у пацієнтів із ЦД2. Своєчасне призначення іНЗКТГ2 (ДАПА 10 мг/добу або ЕМПА 10-25 мг/добу) у складі БМТ є ефективним, патогенетично обґрунтованим алгоритмом лікування з вираженими гепатопротекторними властивостями.

Ключові слова: цукровий діабет 2-го типу, інсулінорезистентність, неалкогольний стеатогепатит, фетуїн-А, інгібітори натрійзалежного котранспортера глюкози 2 типу, дапагліфлозин, емпагліфлозин.

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