Research Article

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Efficacy of Treatment Regimens for Sodium-Glucose Counter Transporter 2 Inhibitor (Emaglyf) with Metformin and DPP-4 Inhibitor (Januvia) in Patients with Type 2 Diabetes Mellitus with Stage 1-3 Chronic Kidney Disease

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SUMMARY

Purpose of the Study: To study the effectiveness of combination therapy of sodium-glucose counter transporter 2 inhibitor -SGLT-2 - (Emaglyf) with metformin and DPP-4 inhibitor (Januvia) in patients with stage 1-3 chronic kidney disease associated with DM 2

Material and Research Methods: A total of 40 patients with DM 2 and CKD grades 1-4 were selected. To study the effect of various schemes of nephroprotective therapy on the functional state of the kidneys in t DM 2, patients were divided into 2 therapeutic groups:

- Group 1 consisted of 20 patients with DM 2 and CKD 1-3 tbsp. receiving SGLT-2 (emoglyph) + metformin
- Group 2 consisted of 20 patients with DM 2 and CKD 1-3 tbsp. receiving SGLT-2 (Emoglyph) + DPP 4 (Januvia).

In the work, general clinical, clinical and biochemical (AL, AST, bilirubin, PTI, urea, creatinine, GFR, C-reactive protein, etc.), hormonal (insulin, C-peptide), immunological (uromodulin) methods of blood tests, as well as instrumental methods of examination - ultrasound of internal organs, Ultrasound and dopplerography of renal vessels, as well as statistical methods. We also evaluated the results of ECG in 12 conventional leads and echocardiography (EchoCG) (dimensions of the chambers of the heart, the thickness of its walls and myocardial contractility). The control group consisted of 20 healthy individuals.

Research Results: The initial data of carbohydrate metabolism indicated its decompensation in the studied groups. There were no significant differences between the Doppler values of the renal arteries in the groups. At the same time, the indicators significantly differed from those of the control group.

Conclusions:

1) After 6 months of therapy, the indicators of carbohydrate metabolism reached normalization in both groups, while the best results were observed when using the SGLT-2 + DPP4 regimen.

2) After 6 months of treatment, significant differences were found between the Doppler values of the renal arteries in the groups, namely, when using the SGLT-2 + DPP4 scheme.

Keywords: Diabetes Mellitus 2; CKD Stage 1-3; Januvia; Emaglyph; Metformin

Background

As is known, the general goals of the treatment of type 2 diabetes mellitus (DM 2) are to avoid acute metabolic decompensation, prevent or delay complications, reduce premature mortality and maintain quality of life [1]. Pharmacological treatment options for T2DM are divided into:

a) Non-insulin therapies, including

1) Insulin sensitizers (metformin, thiazolidinediones [TZDs]).

2) Secretion stimulants (sulfonylureas [SUs]).

3) Incretin-based therapies (receptor agonists glucagon-like peptide-1 [RAs GLP-1], dipeptidyl peptidase-4 inhibitors [DPP4-is]), and

4) Insulin-sparing agents such as α-glucosidase inhibitors (AGis) and sodium glucose cotransporter-2 inhibitors (SGLT-2is); and

b) Insulin therapy. Until recently, stepwise and combination therapy were the two guidelines for pharmacological approaches in T2DM [2-5]. Due to the lack of sufficient data on the use of early combination therapy, stepwise treatment intensification has been the standard approach to achieve glycemic control, as recommended by the ADA/EASD consensus treatment algorithm. Asia, China, Hong Kong, Taiwan, Korea and Japan follow similar rules [6].

The AACE and ADA/EASD guidelines recommend intensifying treatment with an additional drug if monotherapy fails to achieve or maintain the target HbA1c level after 3 months. Preferred third-line therapy includes insulin or a triple combination of oral antidiabetic drugs [5,6]. The AACE treatment algorithm recommends that patients with an HbA1c level of 7.5% or higher (≥59 mmol/mol) be started on combination therapy with metformin plus an additional antidiabetic agent [5]. The 2018 ADA/EASD Position Statement recommends combination treatment only if HbA1c is more than 17 mmol/mol (1.5%) above an individual's target [7]. In line with the latest data, the 2019 update recommends early recruitment of patients with newly diagnosed T2DM to start combination therapy through shared decision making. [four]. In Taiwan, combination therapy with metformin and another antidiabetic drug is recommended for patients with an HbA1c level of 8.5% or higher (≥69 mmol/mol) at the time of diagnosis [8]. In Hong Kong and Korea, combination therapy with metformin is recommended for patients with HbA1c 7.5% or higher (≥59 mmol/mol) [9,10].

Almost all classes of hypoglycemic drugs, such as metformin, SU, AGi, GLP-1 RA, DPP4-i, and SGLT2-i, can be used in combination. Most early combination therapies use metformin as baseline therapy. The efficacy and safety of various combination therapies have been reviewed and evaluated in detail in meta-analyses [11,12]. Positive Effects of SGLT2 on the kidneys was first shown in the EMPAREG, CANVAS and DECLARE cardiovascular trials (CVOT). These studies initially focused on assessing cardiovascular safety in patients with type 2 diabetes with renal outcomes as a secondary endpoint [Barnett AH, et al. 2014]. The efficacy and renal outcomes of SGLT2 inhibitors in patients with type 2 diabetes mellitus and chronic kidney disease were studied in a 2019 US multicenter study [Michael S, et al. 2019]. However, the effectiveness remains unexplored. SGLT2 in combination with other drugs at the stage before hemodialysis in patients with DM 2 and CKD. The above was the reason for the present study.

Purpose of the Study

To study the effectiveness of combination therapy of sodium-glucose counter transporter 2 inhibitor -SGLT-2- (Emaglyf) with metformin and DPP-4 inhibitor (Januvia) in patients with stage 1-3 chronic kidney disease associated with DM2.

Material and Research Methods

A total of 40 patients with type 2 diabetes and CKD grades 1-4 were selected. To study the effect of various schemes of nephroprotective therapy on the functional state of the kidneys in DM2, patients were divided into 2 therapeutic groups:

- Group 1 consisted of 20 patients with DM 2 and CKD 1-3 tbsp. receivingSGLT-2 (emoglyph) + metformin.
- Group 2 consisted of 20 patients with DM 2 and CKD 1-3 tbsp. receivingSGLT-2 (Emoglyph) + DPP 4 (Januvia)

In the work, general clinical, clinical and biochemical (AL, AST, bilirubin, PTI, urea, creatinine, GFR, C-reactive protein, etc.), hormonal (insulin, C-peptide), immunological (uromodulin) methods of blood tests, as well as instrumental methods of examination - ultrasound of internal organs, Ultrasound and dopplerography of renal vessels, as well as statistical methods. We also evaluated the results of ECG in 12 conventional leads and echocardiography (EchoCG) (dimensions of the chambers of the heart, the thickness of its walls and myocardial contractility). The control group consisted of 20 healthy individuals. For kidney ultrasound, an Aloka ultrasound machine with a 4L convex probe (2–5 MHz) was used. The renal resistive index in segmental arteries was assessed as described by the authors. The average value of RI was calculated from 2-3 measurements in the upper, middle and lower sections of the renal sinus. Renal perfusion was assessed using the DTPM method.

The renal artery was assessed at seven points: at the exit from the aorta, in the proximal, middle and distal segments, as well as the apical, middle and inferior segmental arteries. Peak systolic (PSV) and end diastolic (EDV) blood flow velocities, resistivity index (RI), acceleration time (AT), acceleration index (PSV/AT) were calculated. Statistical processing was carried out on a personal computer using the Microsoft Excel-2019 software package using the methods of parametric and non-parametric statistics. With mild renal failure (GFR> 50 ml / min, approximately corresponding to the content of serum creatinine <1.7 mg / dl in men, <1.5 mg / dl in women) Januvia dose adjustment is not required. In moderate renal failure (GFR >30 mL/min but <50 mL/min, roughly corresponding to serum creatinine >1.7 mg/dL but <3 mg/dL in men, >1.5 mg/dL, but <2.5 mg/dl in women) the dose of Januvia is 50 mg 1 time per day. When taking Emaglif, it is recommended to monitor kidney function before starting treatment (at least once a year), as well as before prescribing concomitant therapy that may adversely affect kidney function. Patients with renal insufficiency less than 45 ml / min / 1.73 m^2) receive Emaglyf is contraindicated.

Research Results and Discussion

Table 1 shows the distribution of patients by sex and age. As can be seen from Table 1, patients in the age group from 45 to 74 years old both among men and women predominated - 25/15 cases, respectively. Table 2 gives general characteristics of patients included in the study in groups. As can be seen from Table 2, there were no significant differences in the general characteristics of the initial indicators in the studied groups (p>0.05). The mean glomerular filtration rate (GFR) was significantly lower in all groups. Next, we studied the biochemical parameters by groups before treatment (Table 2). As can be seen from Table 2, the initial data on carbohydrate metabolism indicated its decompensation in the studied groups. The next step was to conduct dopplerography of the renal arteries before and after treatment (Table 3). As seen from the data shown in Table 3 showed significant differences between the Doppler values of the renal arteries in the groups compared to the control. After 6 months of treatment according to the above schemes, we studied the effectiveness of therapy in the study groups, for which we studied the dynamics of biochemical and Doppler parameters (Tables 4 & 5). As can be seen from Table 4, after 6 months of therapy, the indicators of carbohydrate metabolism reached normalization in both groups, while the best results were observed in group 2 patients. The next step was to conduct dopplerography of the renal arteries before and after treatment (Table 5).

Table 1: Distribution of patients by sex and age.

Age, years	Number of men	Number of women
18-44 (young age)	-	-
45-59 (average age)	7 (28.0%)	9 (60.0%)
60-74 (old age)	18 (72.0%)	6(40.0%)
75 and older (old age)	-	-
Total: n=40	25 (62.5%)	fifteen(37.5%)

Table 2: Mean biochemical blood parameters of patients by groups before treatment

Group	blood sugar* mmol/l	HbA1C, %	Postprandial
1 group n=20	13.7*± 0.7	9.6*±1.4	16.3*± 4.3
2 group n=20	15.6*± 0.3	9.8*± 1.5	17.4* ± 3.2

Note: P - significance of differences compared with control data, where * - p <0.05.

As can be seen from the data, given in Table 5, after 6 months of treatment, between the Doppler values of the renal arteries in the groups, a significant improvement in the parameters was revealed.peak systolic (PSV) and end-diastolic (EDV) blood flow velocity, resistivity index (RI), acceleration time (AT), acceleration index (PSV/AT),namely, in group 2, the best results were obtained (in comparison with control data p>0.05). Thus, our study showed nephroprotective effect of both schemes. Our results confirm the literature data. Thus, according to Italian authors, antidiabetic drugs with potential nephroprotective effects, namely DPP-4 inhibitors, incretin analogues and SGLT-2 inhibitors, can have a nephroprotective effect regardless of glycemic control. Sodium-glucose co-transporter (SGLT) 2 inhibitors act at multiple sites

that may affect kidney function, according to other sources. The canagliflozin Cardiovascular Assessment Study (CANVAS) showed a 27% reduction in albuminuria progression, a 40% reduction in eGFR, need for renal replacement therapy, or death from renal causes associated with canagliflozin use. All of the above confirms the high relevance of this study and dictates the need for its further continuation.

Table 3: Doppler parameters of the kidneys in patients included in the study (M ± m).

Index	I group(n=20)	II group(n=20)	Control	R
peak systolic blood flow velocity in the right renal artery (PSV), cm/s	77.3±6.2	75.2 ± 8.4	100±20	<0.05
end diastolic (EDV) blood flow velocity in the right renal artery, cm/sec	15.2±1.2	13.2±1.4	25-50	<0.05
hilum resistivity index (RI)	3.2±0.3	3.5±0.9	<0.8	<0.05
resistance index on intrarenal arteries (RI)	1.6±0.7	1.9±0.3	0.34-0.74.	<0.05
acceleration time (AT), msec	77.2 ± 8.3	72 ± 6.2	46 -55	<0.05
acceleration index (PSV/ AT).	1.8±0.7	1.7±0.6	0.3–0.8	<0.001

Table 4: Mean biochemical blood parameters of patients by groups after 6 months of treatment.

Group	blood sugar * mmol/l	HbA1C, %	Postprandial glycemia,mmol/l
1 group n=20	8.3*± 0.2	6.4*±0.8	9.3*± 1.2
2 group n=20	6.3**± 0.4	6.2**± 0.3	7.3** ± 0.9

Note: P - significance of differences compared with control data, where * - p <0.05. , **-p<0.001 after 6 months of treatment.

Table 5: Doppler parameters of the kidneys in patients included in the study (M ± m).

Index	I group(n=20)	II group(n=20)	Control	R
peak systolic blood flow velocity in the right renal artery (PSV), cm/s	92.5±11.7	87.9 ± 9.7	100±20	>0.05
end diastolic (EDV) blood flow velocity in the right renal artery, cm/sec	38.8±9.3	33.9±8.1	25-50	>0.05
hilum resistivity index (RI)	0.9±0.006	0.8±0.004	<0.8	>0.05
resistance index on intrarenal arteries (RI)	0.5±0.004	0.7±0.004	0.34-0.74.	>0.05
acceleration time (AT), msec	51.5 ± 5.8	49.7 ± 4.9	46 -55	>0.05
acceleration index (PSV/ AT).	0.7 ± 0.003	0.5 ± 0.002	0.3–0.8	>0.05

Conclusion

1) After 6 months of therapy, the indicators of carbohydrate metabolism reached normalization in both groups, while the best results were observed when using the SGLT-2 + DPP4 regimen.

2) After 6 months of treatment, significant differences were found between the Doppler values of the renal arteries in the groups, namely, when using the SGLT-2 + DPP4 scheme.

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