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Effectiveness of Empagliflozin Use in Patients with Diabetes Mellitus Type 2

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Abstract

It has been proved the effectiveness of empagliflozin use in preventing the key cardiovascular risk factors in patients with diabetes mellitus type 2, with normal weight and overweight, who had gotten metformin. An SGLT2 inhibitor empagliflozin decreases statistically body weight in patients with overweight and decreases statistically carbohydrate metabolism indices, systolic blood pressure, as well as leptin level in patients with normal weight and overweight.

Keywords: Diabetes Mellitus Type 2; Empagliflozin; Hyperleptinemia; Cardiovascular Risk Factors

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Introduction

Cardiovascular morbidity increases notably among patients with diabetes. According to the WHO evaluations, 17 billion (30% from all death cases) die from cardiovascular diseases (CVD) every year [1]. According to recent data, CVDs cause more than 4 billion deaths along with the whole of Europe every year that is 45% of all deaths. Herewith the CVDs are 49% of all deaths in females and 40% of all deaths in males. But according to recent data, mortality from the CVDs decreased in 12 European countries [2]. It is important to notice that in the last decades, there is sufficient evidence basis of that increased CVD risk occurs in a (very) young age.

A correlation between leptin resistance and cardiovascular risk was found in patients with arterial hypertension and metabolic syndrome [3].

Apart from overweight, hyperleptinemia has been also associated with hypertension and insulin resistance [3-8]. The peripheral actions of leptin include stimulation of inflammatory reaction, oxidative stress, atherogenesis, and thrombosis, thus promoting endothelial dysfunction, arterial stiffness, development and vulnerability of atherosclerotic plaques [8-13]. Furthermore, leptin regulates bone homeostasis, reproduction, and angiogenesis [14]. There is a positive correlation between leptin levels in blood and insulin sensitivity, body mass index, waist circumference, hyperglycemia [15]. Elevated leptin concentrations have also been related to the incidence and progression of chronic kidney disease as well as insulin resistance, T2DM, micro- and macrovascular diabetic complications. Statins and antidiabeticdrugs (including sitagliptin, metformin, pioglitazone, liraglutide, and empagliflozin) may affect leptin levels [16].

According to the American Diabetes Association (ADA, 2020) and the European Society of Cardiology (ESC, 2019) guidelines, it is appropriate to use SGLT2 inhibitors and GLP-1 agonists as first- and second-line drugs for patients with atherosclerosis and high risk orpresence of heart failure [17,18]. It is necessary to mention that according to the EMPA-REG OUTCOME study, empagliflozin decreased significantly statistically cardiovascular (by 38%) and general (by 32%) mortality. Besides that, the number of hospitalizations due to heart failure decreased by 35% [19]. During the whole study period, empagliflozin intake was associated with decreasing in body weight, waist circumference, uric acid level, systolic blood pressure (SBP) compared to placebo without increased heart rate, however with the mild, but statistically significant increase of HDL level [20]. Schernthaner G. et al. suggest that the addition of both empagliflozin and pioglitazone to metformin might be relatively the best option to reduce high cardiovascular morbidity and mortality of patients with T2DM and already present cardiovascular complications [21].

However at the moment, there are no data about the influence of empagliflozin on leptin level, empagliflozin effectiveness against key cardiovascular risk factors in diabetic patients with normal weight and overweight has not been studied yet.

Material and Methods

In the Department of Therapy No1 of Ivano-Frankivsk Central City Clinical Hospital, 60 patients with DM type 2 (WHO criteria 1999) were examined, who were getting metformin for not less than 6 months, but had not reached the HbA1c target (at the moment of inclusion into the study > 7.5%, but < 9%), as well as 10 practically healthy people.

The patients' average age was 46.9±3.2 years. The patients had no cardiovascular diseases and complications except AH in anamnesis and at the time of examination. The patients were not included in the study, if they had GFR<60 mL/min/1.73 m^2, rare genetic disorders (lactase deficiency, lactose intolerance, glucose-galactose malabsorption), as well as other contraindications for empagliflozin indicated in its instruction on application.

All patients got the general clinical examination that included the measure of height, weight, body mass index (BMI) or Quetelet's index, waist circumference (WC), blood pressure (BP). Total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C) levels in blood serum were determined with the fermentation method. Low-density lipoprotein cholesterol (LDL-C) levels were calculated using the Friedewald formula. Carbohydrate metabolism was evaluated by blood glucose and glycated hemoglobin levels. We performed general cardiovascular risk stratification depending on systolic blood pressure (SBP), diastolic blood pressure (DBP), risk factors, asymptomatic target organ damage, DM, chronic kidney disease and cardiovascular diseases which had manifested clinically according to ESH (2019) [18]. Leptin levels (3.7-11.1 ng/ml in norm) were determined with the help of the Diagnostics Biochem Canada Inc kit. Obligator instrumental examination included blood pressure measuring. Anthropomorphic characteristics were determined with the evaluation of body mass index (BMI) calculated using the Quetelet's formula (BMI=BW/H2, where BW is the body weight, kg; H is the height, m). To find out the obesity type, the waist-to-hip ratio was calculated. To control fasting carbohydrate metabolism, glucose concentration was evaluated by the glucose oxidase method. The endogenous insulin (EI) level was determined by enzyme-linked immunosorbent assay with the DRG Diagnostics tests (Germany). Insulin resistance was assessed with the HOMA-IR = (fasting glucose (mmol/L) x fasting insulin (мкМО/ml))/22.5).

Statistical analysis was performed by analysis of variance. While analyzing materials, we calculated means (M), their standard errors (m), and confidence interval. Statistical significance was evaluated with Student's t-test for dependent and independent samples; nonparametric Mann-Whitney U, Wilkonson W tests were used at the irregularity in the distribution. Differences were considered probable at p<0.05.Association between variables was evaluated by Spearman's rank correlation. Statistical data processing was performed with the help of variational and descriptive statistics using standard analytics packages Statistica 6.0, Foxbase, Exel 6.0 on the personal computer Pentium III.

Result and Discussion

The patients were randomized in 2 groups dependently on BMI. Group I consisted of 29 patients with BMI<24.9 kg/m^2 (23.7±0.22), group II had 31 patient with BMI>24.9 kg/m^2 (27.83±0.38). Leptin, lipid panel, insulin resistance values for the patients of these groups are presented in Table 1.

During the examination of the patients, we found out that in group I high cardiovascular risk was in 70.6% of females, very high one was in 29.4%; in group II high risk was in 64.7% and very high one in 35.3% of women. Among males (group I), 75% had high cardiovascular risk and 25% very high one, whilst in group II 66.6% had high, and 33.4% very high risk. In patients of both groups, there was a correlative association between leptin levels and cardiovascular risk factors. The data we received correspond to Mitchenko OI, et al. (2015) studies [3].

Table 1: Leptin, lipid panel, insulin resistance values in patients with diabetes mellitus type 2 dependently on BMI, (M±m).

Value	Practically healthy (n=10)	Group I, BMI<24.9 kg/m^2 (n=29)	Group II, BMI>24.9 kg/m^2 (n=31)
TC, mmol/L	4.09±0.18	5.16±0.25*	5.94±0.31*
TG, mmol/L	1.20±0.9	4.86±0.35*	6.68±0.51*
LDL-C, mmol/L	1.68±0.11	3.76±0.003*	3.02±0.37*
HDL-C, mmol/L	1.42±0.15	1.01±0.05*	0.82±0.06*
WC, cm, f	76.64±0.34	86.73±0.89*	102.8±1.49*
m	90.08±0.52	97.43±0.48*	118.43±2.2*
BMI, kg/m^2	22.7±1.12	23.7±0.22	27.83±0.38*
HOMA-IR	2.32±0.06	4.46±0.92 *	8.05±0.99 *
Leptin, ng/ml	5.4±1.56	11.05±1.3*	27.37±3.2*
Note: *probable difference relative to the values in practically healthy people (p<0.05)			
Probable difference between values in the patients of groups I and II, p<0.05			

Dependently on administered treatment, all patients were randomized into 4 groups (Table 2). All included into the study patients were administered with the hypocaloric diet with limited intake of easily digested carbohydrates and saturated fats (1800 kcal/day, daily calorie intake was calculated by the formula recommended by WHO (1998) for each patient individually), besides that they were recommended to extend physical activity (walking 5 thousand steps per day). The patients of groups IA and IIA got metformin in individual doses as basic therapy.The patients of groups IB and IIB were administered empagliflozin 10 mg/day besides metformin.

Table 2: Distribution of patients dependently on treatment scheme.

Group I, BMI<24.9 kg/m^2	**Group IA (n=14)** **(9 females, 5 males)** basic therapy	**Group IB (n=15)** **(8 females, 7 males)** basic therapy + empagliflozin 10 mg/day
Group II, BMI>24.9 kg/m^2 (n=45)	**Group IIA (n=15)** **(8 females, 7 males)** basic therapy	**Group IIB (n=16)** **(9 females, 7 males)** basic therapy + empagliflozin 10 mg/day

The patients continued taking administered earlier hypotensive, hypolipidemic therapy during the whole study without its correction.

After the 6-month treatment course with using SGLT2 inhibitors was done, the positive key cardiovascular risk factors dynamics was observed. So, the SBP and DBP values dynamics was more expressed in examined patients under the influence of the complex therapy with using of empagliflozin compared to the basic therapy as in males, as well as in females. Especially, SBP decreased by 11.82% (p<0.05) in group IB and by 12.4% (p<0.05) in group IIB and DBP decreased by 8.15% (p<0.05) and 8.3% (p<0.05) that was less expressed in groups of comparison. Under the influence of the therapy course, positive dynamics of carbohydrate metabolism which was probable in the patients of groups IB and IIB who were taking SGLT2 inhibitor additionally compared to the patients of groups IA and IIA (table 3). For example, in the patients of group IB fasting glycemia decreased by 27.19% (p<0.05), HbA1c by 10.13% (p<0.05); in the patients of group IIB by 16.28% (p<0.05) and HbA1c by 11.1% (p<0.05) respectively (Table 3).

In our opinion, probable decrease by 41.9%(p<0.05) of HOMA IR in the patients of group IIB was important; in other groups, probable changes were not found (Table 3). In the process of treatment, BMI decrease was observed in not all groups. In the patients of groups IA and IB, probable dynamics in decreasing weight was not observed (Table 3). So, in group's IA and IB, BMI decrease was unreliable and did not depend on received therapy (p > 0.05). In group IIA there was no probable BMI decrease (p > 0.05); unlike in group IIA, in group IIB

Table 3: Metabolic parameters in examined patients with DM type 2, M±m.

Parameter	Therapy duration	Group I, n = 29		Group II, n = 31	
		IA, n = 14	IB, n = 15	IIA, n = 15	IIB, n = 16
BMI, kg/m^2	Before Therapy	24.1±1.55	23.8 ± 1.81	27.80±0.33	27.82±0.35
	6 Months	23.34±0.39	22.76±0.34	27.84±0.55	25.1±0.50*
WC, cm, f	Before Therapy	77.25±1.55	77.5±1.48	103.2±1.42	103.12±1.78
	6 Months	75.13±1.56	73.5±1.54*	101.75±2.18	97.86±1.98*
WC, cm, m	Before Therapy	86.0±1.47	85.4±0.81	119.0±2.96	119.67±1.05
	6 Months	84.25±1.44	82.6±0.68*	118.0±1.87	115.5±1.31*
HbAlc, %	Before Therapy	7.82±0.41	7.9±0.37	8.0±0.49	8.1 ± 0.49
	6 Months	7.6±0.44	7.1±0.39*	7.8±0.54	7.2 ± 0.47*
HOMA IR	Before Therapy	4.46±0.93	4.39±0.82	7.97±1.62	8.13±1.98
	6 Months	4.44±0.91	3.21±0.88	7.75±1.28	4.72±1.59*
Leptin, ng/ml	Before Therapy	10.84±1.45	11.26±1.38	27.12±2.48	27.62±2.48
	6 Months	9.55±1.55	6.81±1.61*	27.56±2.21	19.6±1.21*
TC, mmol/L	Before Therapy	5.17±0.24	5.14±0.27	5.91±0.31	5.93±0.36
	6 Months	5.16±0.25	5.16±0.26	5.90±0.33	5.94±0.32
LDL-C, mmol/L	Before Therapy	3.76±0.003	3.75±0.003	3.03±0.37	3.01±0.37
	6 Months	3.75±0.004	3.76±0.005	3.02±0.41	3.04±0.39
HDL-C, mmol/L	Before Therapy	1.00±0.04	1.02±0.05	0,82±0.06	0.83±0.05
	6 Months	1.01±0.05	1.03±0.04	0,81±0.07	0.82±0.08
TG, mmol/L	Before Therapy	4.85±0.35	4.86±0.34	6,67±0.52	6.68±0.53
	6 Months	4.84±0.36	4.89±0.38	6,63±0.51	6.70±0.56

Note: * difference is probable compared to the value before treatment.

BMI decrease was probable from 27.82±0.35 to 25.1±0.50 ($p < 0.05$) (Table 3). But WC decreased reliably ($p < 0.05$) as in males, as well as in females of groups IB and IIB (Table 3). While analyzing received results, we noticed the probable influence of empagliflozin on the leptin level. So, in patients with normal BMI, who got empagliflozin (group IB), it decreased by 39.5% ($p < 0.05$), and the group of patients with overweight (IIB) by 29% ($p < 0.05$) while taking empagliflozin; in groups without empagliflozin reliable dynamics of leptin level was not observed (Table 3). The probable dynamics of lipid profile was not observed in any group (Table 3). Empagliflozin did not influence reliably hepatic values (AST, ALT). By evaluation of empagliflozin safety/tolerance, we also paid attention to serum creatinine / GFR values. Statistically significant changes in these values were not present in our patients. All participants finished the study; nobody from them presented side effects.

Moreover, to evaluate empagliflozin safety, total urine analyses, in which there were found no statistically significant abnormalities in any participant, were done for the patients on each visit.

The main conclusions of this study show that an SGLT2 selective inhibitor empagliflozin influences key cardiovascular risk factors. Under the influence of empagliflozin, systolic blood pressure improves; glycemia indices reliably decrease, independently on BMI. Importantlyno patient had hypoglycemia that was confirmed by other authors too [19-23]. Several authors point out the pleiotropic effect of empagliflozin on the improvement of cardiac activity in animals with obesity without diabetes [24-26]. Recently published new data show that in the post-myocardial infarction setting, empagliflozin had major beneficial effects on the principal load-independent measures of systolic function, preload recruitable stroke work and end-systolic pressure-volume relationship. In these non-diabetic animals, empagliflozin did not affect glycemia, as assessed by HbA1c, in both sham and post-MI groups [25]. Empagliflozin improves diastolic function in a nondiabetic rodent model of heart failure with preserved ejection fraction too [26].

An important cardiovascular risk factor is weight. But the problem of using of SGLT2 inhibitors in patients with normal BMI remains debatable. In or std, BMI and HOMA-IR decreased significantly under the influence of empagliflozin only in patients with overweight; the patients with normal BMI got their weight decreased, but not significantly, whereas other studies conducted on animals showed probable weight decrease by empagliflozin intake [25-27]. Possibly, these changes were interrelated with probable leptin level decrease, as well as the influence of empagliflozin on visceral fat. Nedogoda SV, et al. (2018) fond out also the significant influence of empagliflozin on HbA1c levels, chronic non-specific inflammation (including CRP) and immune resistance markers (leptin, HOMA-IR) in patients with DM type 2 and obesity. Several experimental works point out the decrease of TG and TC levels [23,27], other show increased HDL-C. In our study, we did not find out the reliable dynamics of lipid profile in any group.

Conclusion

Using of the SGLT2 inhibitor empagliflozin in the complex therapy of patients with diabetes mellitus type 2 and different bodyweight increase therapy effectiveness by positive dynamics of key cardiovascular risk factors, particularly decrease of body weight, waist circumference, blood pressure, carbohydrate metabolism indices and insulin resistance, leptin in particular.

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