Jordan Journal of Pharmaceutical Sciences, Volume 16, No. 2, 2023

Evaluation of the Effect of Dapagliflozin on CRP Levels in Type 2 Diabetes Patients

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ABSTRACT

Type 2 diabetes mellitus (T2DM) is an increasingly prevalent chronic disease that associates with an increased risk of micro-and macrovascular complications. There is persuasive evidence that dapagliflozin may reduce chronic inflammation besides its glucose-lowering effect, which in term prevents the development of the disease and its complications. Therefore, this study aims to evaluate the effects of dapagliflozin on the inflammatory marker C-reactive protein (CRP) levels in T2DM patients. Patients with T2DM were randomly assigned into two groups, group 1 (n=52) receiving a daily dose of dapagliflozin as an add-on therapy with oral antihyperglycemic agents, and group 2 (control, n=60) who received oral antihyperglycemic agents (Metformin, Sulfonylureas, Thiazolidinediones, and Gliptins). After six months, our results showed a significant change in CRP levels from baseline after receiving dapagliflozin compared to the control. Although the reduction level of CRP was statically significant with both 5 mg and 10 mg doses, it was higher with the latter one. In addition, the reduction in CRP levels was statistically significant in both controlled and uncontrolled, but more important in uncontrolled disease. An insignificant positive correlation was seen between HbA1c and CRP on admission (r: 0.21, p: 0.1) and during the follow-up period, at 3 months (r: 0.10, p: 0.4) and 6 months (r: 0.08, p: 0.5). Our study showed that dapagliflozin has a beneficial effect on inflammation by reducing CRP levels CRP in patients with T2DM.

Keywords: Type 2 diabetes mellitus (T2DM), Dapagliflozin, CRP, inflammation.

INTRODUCTION

Diabetes mellitus (DM) encompasses metabolic disorders that are characterized by hyperglycemia resulting from relative or absolute impairment of insulin secretion with varying degrees of insulin resistance. According to etiology and clinical presentation, DM is classified into three types: type 1 (T1DM), type 2 (T2DM), and gestational (GDM)[1]. The prevalence of DM has increased dramatically over the past four decades. It is considered a worldwide epidemic with increasing obesity and lifestyle alterations[2].

Type 2 diabetes mellitus (T2DM) is a progressive disease that can be divided into four stages: defect in β cell glucose-stimulated insulin secretion, peripheral insulin resistance, β cell compensations, and β cell loss[3]. T2DM has been correlated with increased levels of inflammatory markers, including interleukin (IL-6), tumor necrosis factor-alpha (TNF-α), plasminogen activator inhibitor 1 (PAI-1), C-reactive protein (CRP), and chemokines. Furthermore, factors that are released from adipose tissue (adipokines) stimulate inflammatory activity, which correlates with insulin resistance[4&5]. Increased CRP blood level is considered a sign of systemic inflammation. It is synthesized and secreted primarily in hepatocytes and

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Received: 15/7/2022 Accepted:20/12/2022.
DOI: https://doi.org/10.35516/jjps.v16i2.1331

regulated by IL-6, IL-1, and TNF-α [6].

Early initiation of diabetes treatment is associated with improved glycemic management and decreased long-term complications[7]. Sodium-glucose co -transporter-2 inhibitors (SGLT2i) are new drugs that promote the renal excretion of glucose and thereby lower high-risk blood glucose levels in patients with T2DM[8]. Currently, there are three FDA-approved SGLT2 selective inhibitors for the treatment of T2DM: canagliflozin, dapagliflozin, and empagliflozin[9]. The anti-inflammatory properties of dapagliflozin may possess therapeutic benefits beyond their glucose-lowering activity. Several mechanisms explain the anti-inflammatory effect of dapagliflozin including a reduction in adipose tissue inflammation, weight loss, mild increase in ketone bodies, and attenuation of oxidative stress[10]. The objective of this study was to investigate changes in CRP levels during treatment with dapagliflozin in T2DM patients.

MATERIALS AND METHODS

This is a randomized controlled trial of a group of T2DM patients attending the department of endocrinology at Tishreen University Hospital in Lattakia-Syria from September 2020 to May 2022.

We included male and female patients from different age groups who were diagnosed with T2DM.

On the other hand, we excluded patients with one of the following: chronic inflammatory disease, pathologic obesity, changed or discontinued drugs that affected CRP values during follow-up, acute inflammation when specimen samples were collected and estimated glomerular filtration rate (e GFR) ≤ 30 ml/min/1.73 m².

A questionnaire was designed to record patients' information such as age, weight, height, Body mass index (BMI), current and previous diseases, used medications, and smoking.

The first group included 52 T2DM, who received dapagliflozin as an add-on therapy to oral antihyperglycemic drugs (Metformin, Sulfonylureas, Thiazolidinediones, and Gliptins). The second group (control) included 60 T2DM, who were on oral antihyperglycemic drugs (Metformin, Sulfonylureas, Thiazolidinediones, and Gliptins). Patients in group I were on a daily dose of either 5 mg (27 cases) or 10 mg (25 cases) of dapagliflozin. Patients were on the same medication regimen during the follow-up period without adding any drug that can affect CRP values such as oral contraceptives or statins.

Body mass index (BMI) was calculated as (weight/height^2) (kg/m^2) and categorized as normal weight (18.5-24.9 kg/m^2), overweight (25-29.9 kg/m^2), and obesity (≥30 kg/m^2). Patients were divided according to the 10-year atherosclerotic cardiovascular disease (ASCVD) risk score developed by the American College of Cardiology/American Heart Association (ACC/AHA) into a low-risk group if ASCVD score was ≤7.5% and a high-risk group if ASCVD score was >7.5%. Glycated hemoglobin (HbA1c) was considered as a marker of good glycemic control if HbA1c was <7% and poor glycemic control if HbA1c was >7%. CRP levels were measured in all patients at baseline, after 3 months, and after 6 months.

Biochemical evaluation:

Venous blood samples were taken in the morning after fasting for at least 8 hours overnight.

Laboratory assessments included:

1. C reactive protein (CRP) levels were measured by turbidometric method using an automated analyzer (BS-380, Mindary) normal range: < 5 mg/L.
2. Fasting plasma glucose levels were measured by colorimetric method using an automated analyzer (BS-380, Mindary) normal range: 70-110 mg/dL
3. Glycated hemoglobin HbA1c was measured by fluorescent immunoassay technology (Diabetes >6.5%) by an automated analyzer (Finecare, Wondfo).

Ethical approval: All procedures were approved by the Institutional Review Board of Tishreen University. The decision involved Ethical Approval (Decision Number: 2874 in September 2020). Informed verbal consent was taken from each participant in the study.

Statistical Analysis:

Statistical analysis was performed using IBM SPSS version20. Basic Descriptive statistics included means, standard deviations (SD), median, frequency, and percentages. For relationships and comparisons between two groups, the chi-square test or Fisher exact test was performed. An Independent t-student test was used to compare 2 independent groups. The Friedman test was used to detect differences between groups when the dependent variable being measured was ordinal. All tests were considered significant at a 5% type I error rate (p<0.05), β: 20%, and power of the study: 80%.

RESULTS

Study's group included 112 patients (51 male, 61 female) with T2DM. Age ranged from 39 to 70 years, with a mean age of 54.8±7.7 years, BMI ranged from 18.73 to 35 kg/m² with a mean value of 28.1±3.6 kg/m², and HbA1c ranged from 4.20 to 11.20 mg/dL with a mean value of 7.50±1.3 mg/dL.

The baseline characteristics of patients are shown in Table (1). No significant differences were found between groups in terms of age, gender, BMI, smoking, comorbidities, and drugs (p>0.05) except for using statins, which was more frequent in group II (45% versus 23.1%, p: 0.01). In group I, the mean age was 56.15±7.9 years, and the most frequent age group was 50-59 years (40.4%), followed by ≥ 60 years (34.6%) and 40-49 years (25%). Males represented 42.3% and females represented 57.7% of the patients. Mean value of BMI was 28.21±3.5 kg/m². Overweight patients represented the most frequent group (46.2%), followed by obesity (34.6%) and normal weight (19.2%). Hypertension was present in 40 cases (76.9%) and the mean duration of the disease was 4.08±3.74 years. Regarding frequencies of antidiabetic agents, 94.2% of the patients were on metformin, 50% were on sulfonylurea, 23.1% were on dipeptidyl peptidase inhibitors, and 1.9% were on thiazolidinediones. Patients were classified according to ASCVD score into low-risk (31 cases: 59.6%) or high-risk (21 cases: 40.4%). In group II, the mean age was 53.73±7.5 years, and the most frequent age group was 50-59 years (48.3%), followed by 40-49 years (28.3%), and ≥ 60 years (23.3%). Males represented 48.3% and females represented 51.7% of the patients. Mean value of BMI was 28.12±3.8 kg/m². Overweight patients represented the most frequent group (55%), followed by obesity (28.3%) and normal weight (16.7%). Hypertension was present in 36 cases (60%) and the mean duration of the disease was 3.5±2.49 years. All patients were on metformin, 46.7% were on sulfonylurea, 23.3% were on dipeptidyl peptidase inhibitors, and 1.7% were on thiazolidinediones. Patients were divided into low-risk in 37 cases (61.7%) and high-risk in 23 cases (38.3%).

Table 1. Comparison of demographic characteristics of the study groups.

Variables	Group I	Group II	*P*-value
	Dapagliflozin (n=52)	Control (n=60)	
Age (years)	56.15±7.9	53.73±7.5	0.1
Age group (years)			
40-49	13(25%)	17(28.3%)	0.4
50-59	21(40.4%)	29(48.3%)	
≥ 60	18(34.6%)	14(23.3%)	
Sex			
Male	22(42.3%)	29(48.3%)	0.5
Female	30(57.7%)	31(51.7%)	

Variables	Group I	Group II	*P*-value
	Dapagliflozin (n=52)	**Control (n=60)**	
BMI (kg/m2)	28.21±3.5	28.12±3.8	0.9
BMI group			
Normal weight	10(19.2%)	10(16.7%)	0.3
Overweight	24(46.2%)	33(55%)	
Obesity	18(34.6%)	17(28.3%)	
Smoking	26(50%)	34(56.7%)	0.4
Comorbidities			
• Hypertension	40(76.9%)	36(60%)	0.05
Duration (year)	4.08±3.74	3.5±2.49	0.08
• Coronary artery disease (CAD)	5(9.6%)	5(8.3%)	0.8
Oral antihypertensive drugs			
ACE inhibitors	12(23.1%)	10(16.7%)	0.3
Angiotensin receptor blockers (ARBs)	16(30.8%)	14(23.35)	0.3
Beta-blocker	14(26.9%)	9(15%)	0.1
Calcium channel blockers	10(19.2%)	12(20%)	0.9
Diuretics	6(11.5%)	6(10%)	0.7
Others			
Aspirin	6(11.5%)	8(13.3%)	0.7
Statins	12(23.1%)	27(45%)	0.01
Oral hypoglycemic drug			
Metformin	49(94.2%)	60(100%)	0.1
Sulfonylurea	26(50%)	28(46.7%)	0.5
Thiazolidinediones	1(1.9%)	1(1.7%)	0.9
Dipeptidyl peptidase inhibitors	12(23.1%)	14(23.3%)	0.3

The data was analyzed using Chi-Square test or Fisher exact test, $^{*}p$-value ≤ 0.05.

As shown in table (2), no significant difference was found in group I depending on the dose (5 mg or 10 mg) regarding age, gender, BMI, presence of comorbidities, duration, drugs, and the degree of diabetes control ($p>0.05$). Patients on dapagliflozin (5 mg) group were divided into low-risk in 15 cases (55.6%) and high-risk in 12 cases (44.4%), whereas patients on dapagliflozin (10 mg) group were assigned into low-risk in 16 cases (64%) and high-risk in 9 cases (36%), without significant difference between two groups ($p>0.05$).

Table 2. Comparison of demographic characteristics of dapagliflozin group based on dapagliflozin dose.

Variables	Group I		*P*-value
	Dapagliflozin 5 mg (n=27)	Dapagliflozin 10 mg (n=25)	
Age (years)	57.18±7.8	55.04±8	0.3
Sex			
Male	13(48.1%)	9(36%)	
Female	14(51.9%)	16(64%)	0.3
BMI (kg/m2)	28.10±3.3	28.27±2.2	0.5
Smoking	13(48.1%)	13(52%)	0.7
Comorbidities			
• Hypertension	22(81.5%)	18(72%)	0.4
Duration(year)	4.3±4.25	3.7±3.18	0.3
• Coronary artery disease(CAD)	4(14.8%)	1(4%)	0.1
Oral antihypertensive drugs			
ACE inhibitors	8(29.6%)	4(16%)	0.2
Angiotensin receptor blockers(ARBs)	8(29.6%)	8(325)	0.8
Beta -blocker	8(29.6%)	6(24%)	0.6
Calcium channel blockers	6(22.2%)	4(16%)	0.5
Diuretics	2(7.4%)	4(16%)	0.3
Others			
Aspirin	3(11.1%)	3(12%)	0.9
Statins	5(18.5%)	7(28%)	0.4
Oral hypoglycemic drug			
Metformin	26(96.3%)	23(92%)	0.2
Sulfonylurea	15(55.6%)	11(44%)	0.4
Thiazolidinediones		1(4%)	0.2
Dipeptidyl peptidase inhibitors	8(29.6%)	4(16%)	0.2
Duration of treatment T2DM(years)	4.40±3.01	3.93±2.2	0.5
HbA1c(mg/dl)	7.52±1.2	7.47±1.06	0.8

The data was analyzed using Chi-Square test or Fisher exact test, $^{*}p$-value ≤ 0.05.

As shown in table (3), the mean period between the treatment of T2DM and the study enrolment was 4.18±2.6 years in group I versus 3.57±3.2 years in group II, *p*: 0.2. Patients were divided into three groups according to treatment of the disease; <3, 3 – 7 and ≥7. The vast majority of diabetes cases fall in the category 3-7 in group I (63.5%) and group II (46.7%), without significant difference (*p*: 0.1). Mean HbA1c was 7.50±1.1 mg/dl in group I vs. 7.16±1.2 mg/dl in group II, *P*: 0.1. 31 patients (59.6%) exhibited relatively poor glycemic control at baseline vs. 32 patients (53.3%) in group II.

Table 3. Baseline characteristics of T2DM treatment and HbA1c of study's groups.

Variables	Group I	Group II	*P*-value
	Dapagliflozin (n=52)	Control (n=60)	
Duration of treatment T2DM (years)	4.18±2.6	3.57±3.2	0.2
<3	11(21.2%)	21(35%)	0.1
3 – 7	33(63.5%)	28(46.7%)	
≥7	8(15.4%)	11(18.3%)	
HbA1c (mg/dl)	7.50±1.1	7.16±1.2	0.1
Controlled	21(40.4%)	28(46.7%)	0.5
Uncontrolled	31(59.6%)	32(53.3%)	

The data was analyzed using Chi-Square test or Fisher exact test, $^{*}p$-value ≤ 0.05, HbA1c: hemoglobin glycosylated A1C.

As illustrated in Table 4, our results indicate that effect of dapagliflozin on lowering CRP levels is treatment duration dependent. Mean value of CRP was 4.82±4.1 mg/l at baseline and decreased to 2.23±2.2 mg/l after 6 months (*p*: 0.0001), whereas in control group there was no statistically significant difference in CRP-values during the follow-up duration (*p*: 0.08). Dapagliflozin's effect on CRP is dose-dependent. During follow-up, there was a significant decrease in CRP levels in patients who received a daily dose of 5 mg (2±1.8 mg/l at the end of 6 months vs. 4.26±2.9 mg/l at baseline, *p*: 0.0001), and in patients who received a daily dose of 10 mg (2.44±2.7 mg/l at the end of 6 months vs. 5.35±5.1 mg/l at baseline, *p*: 0.0001). However, the level of decrease was higher in patients who were on a daily dose of 10 mg. Additionally, CRP levels were decreased more significantly after 6 months when HbA1c levels were higher at baseline; 2.14±1.8 mg/l at the end of 6 months vs. 4.04±3.5 mg/l at baseline, *p*: 0.0001 in controlled group, and 2.29±2.5 mg/l at the end of 6 months vs. 5.35±4.5 mg/l at baseline, *p*: 0.001 in uncontrolled group. But the level of decrease was higher in patients with higher HbA1c. When CRP levels were higher at baseline, the decrease in CRP levels was higher after 6 months. In comparison to controlled patients, baseline CRP levels were higher in uncontrolled patients.

Table 4. Comparison of measurements between baseline and six-month treatment

Variables	CRP			
	Baseline	3 months	6 months	*P*-value
Dapagliflozin	4.82±4.1	3.21±3.2	2.23±2.2	**0.0001***
Control	3.74±2.5	3.63±2.5	3.49±2.6	0.08
P-value	0.07	0.4	0.006	
Dapagliflozin				
Controlled	4.04±3.5	2.98±2.3	2.14±1.8	**0.0001***
Uncontrolled	5.35±4.5	3.36±3.7	2.29±2.5	**0.001***
P-value	0.2	0.6	0.8	
Dapagliflozin				
5 mg	4.26±2.9	2.71±1.9	2±1.8	**0.0001***
10 mg	5.35±5.1	4.09±3.18	2.44±2.7	**0.0001***
P-value	0.3	0.2	0.4	

The data was analyzed using Friedman test and Independent T Student, * *p*-value ≤ 0.05.

A relationship between HbA1c and CRP was analysed, and we concluded that with low levels of HbA1c, there was an insignificant decrease in CRP at baseline, 3 months, and 6 months of therapy (r: 0.21, *p*: 0.1), (r:0.10, *p*:0.4), and (r: 0.08, *p*: 0.5).

DISCUSSION

The principal clinical concern with T2DM subjects is the potential development of clinically significant complications and associated morbidity and mortality. Therefore, it is crucial that research should focus on the prevention as well as the treatment of the disease.

The result of the current study revealed that dapagliflozin performed a significant reduction in CRP levels when compared to the control ($p<0.05$). The rate of reduction was higher in patients who received a daily dose of 10 mg more than those who took 5 mg, and in uncontrolled DM. Low levels of HbA1c were associated with an insignificant decrease in inflammation degree, which was represented by decreased CRP levels. These changes may be explained by the following effects of dapagliflozin. Firstly, the drug reduces oxidative stress[10], fibrosis[11], and sympathetic overdrive[12]. Secondly, it stimulates anti-inflammatory macrophages and anti-inflammatory cytokines (IL-10)[13&14]. Finally, it reduces renal pro-inflammatory cytokines (TNFα and IL-6), fibrosis, and apoptosis[15&16]. In addition, there were no confounding factors that may affect the CRP values during follow-up. The rate of using statins was higher in the control than the intervention group, which might explain the low baseline values of CRP in control group. Various studies have provided definitive evidence for the favorable effects of dapagliflozin in decreasing CRP levels. Okamoto et al (2016) conducted a study on 27 obese patients with T2DM who were treated with dapagliflozin 5 mg/day for 12 weeks. Their study showed a significant reduction in CRP levels (ng/ml); 1960±1607 vs. 2814±2410, $p<0.01$[17].

Moreover, a study conducted on T2DM mice revealed that a daily dose of dapagliflozin (1.5 mg/kg) reduced CRP levels significantly ($p<0.001$)[18].

Xue et al (2021) demonstrated in a study carried out on 70 patients with T2DM and ST-segment elevation myocardial infarction (35 cases, 35 controls) a significant decrease in IL-6, TNF-α, and CRP levels in patients who were treated with dapagliflozin 5 mg/day at the first week, followed by 10 mg/day compared to the control group, *p*: 0.001[19].

Alhwiesh et al (2022) showed in a study conducted on 50 T2DM patients in Saudi Arabia significantly lower values of CRP in patients receiving a daily dose of 10 mg of dapagliflozin for 6 months[20].

In contrast to our study, Zaihordin et al (2019) demonstrated in a study conducted in Malaysia on 81 T2DM patients with ischemic heart disease (dapagliflozin: control, 40:41) a significant increase in CRP levels: 6.03 vs. 1.93 at baseline, *p*:0.009[21]. Most of these patients were in a high-risk category, and they were followed up for just 12 weeks, dapagliflozin's anti-inflammatory effect may take a longer time to manifest clearly and statistically significant[21].

In summary, the observed reduction in CRP levels suggests that dapagliflozin contributes to reversing processes related to inflammation which impact insulin sensitivity and cardiovascular disease risk.

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تقييم تأثير داباغليفلوزين على مستويات CRP لدى مرضى الداء السكري من النمط الثاني

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[3] قسم الطب الباطني (الغدد الصم)، كلية الطب البشري، جامعة تشرين، ، الجمهورية العربية السورية.

ملخص

الداء السكري من النمط 2 (T2DM) هو مرض مزمن ينتشر بشكل متزايد ويترافق مع زيادة خطر حدوث مضاعفات على مستوى الأوعية الدموية الصغيرة والكبيرة. هناك أدلة واضحة تثبت أن الداباغليفلوزين قد يخفض الالتهاب المزمن بالإضافة إلى تأثيره الخافض للغلوكوز، مما يمنع تطور المرض ومضاعفاته. تهدف هذه الدراسة إلى تقييم آثار الداباغليفلوزين على مستويات المشعر الالتهابي بروتين سي التفاعلي (CRP) لدى مرضى T2DM. تم تقسيم مرضى T2DM بشكل عشوائي إلى مجموعتين، تألفت المجموعة الأولى من 52 مريضاً الذين تلقوا جرعة يومية من الداباغليفلوزين كعلاج إضافي لخافضات سكر الدم الفموية الأخرى، في حين أن المجموعة الثانية (مجموعة الشاهد) تكونت من 60 مريضاً الذين تلقوا خافضات سكر الدم الفموية (ميتفورمين، سلفونيل يوريا، ثيازوليدين ديون، والغلبتينات). بعد مرور ستة أشهر، أظهرت نتائجنا تغييراً كبيراً هاماً إحصائياً في مستويات CRP بعد المعالجة بالداباغليفلوزين مقارنة مع الشاهد. على الرغم من أن معدل انخفاض CRP كان له دلالة إحصائية هامة عند المرضى المعالجين بجرعة 5 مغ و10 مغ، إلا أنه كان أعلى مع الجرعة الأخيرة. بالإضافة إلى ذلك، كان الانخفاض في مستويات CRP ذو دلالة إحصائية هامة عند كل من المرضى المضبوطين وغير المضبوطين، ولكنه كان أكبر عند المرضى غير المضبوطين. تم ملاحظة وجود ارتباط إيجابي غير هام من الناحية الإحصائية بين HbA1c وCRP عند بداية الدراسة (r: 0.21, p: 0.1)، وأثناء فترة المتابعة عند 3 أشهر (r: 0.10, p: 0.4) وعند 6 أشهر .(r: 0.08, p: 0.5) أظهرت دراستنا أن داباغليفلوزين له تأثير مفيد على المشعر الالتهابيCRP لدى مرضى T2DM.

الكلمات الدالة: داء السكري من النمط الثاني، داباغليفلوزين، البروتين سي التفاعلي، الالتهاب.

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تاريخ استلام البحث 2022/7/15 وتاريخ قبوله للنشر 2022/12/20.