THE VALUE OF USING DAPAGLIFLOZIN SUPPLEMENTATION IN THE MANAGEMENT OF TYPE-II-DIABETES WITH HYPERTENSION: A PRELIMINARY-CROSS-SECTIONAL STUDY IN SULAIMANI- IRAQ

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ABSTRACT

Background

Dapagliflozin is known to have pleiotropic effects that extend to the cardiovascular system and various body organs. The presence of concomitant illnesses and complications such as hypertension with type 2 diabetes may change the magnitude of these pleotropic effects.

Objectives

to test the hypothesis that Dapagliflozin supplementation is of benefit in type 2 diabetes associated with hypertension compared to type 2 diabetes without hypertension.

patients and Methods

In this cross-sectional study, 37 diabetic patients who were receiving 10 mg of Dapagliflozin/day plus insulin and/or oral antidiabetic agents were divided into two groups: Group I (n = 15) included diabetic normotensive patients, while group II (n = 22) were diabetic hypertensive patients who were receiving one or two antihypertensive drugs as well. Anthropometric measurements, blood pressure, arterial stiffness index, myocardial work stress, hematological indices, serum fasting lipid profile, glycaemic indices, renal function tests, and Echocardiography for measuring Left Ventricular Ejection Fraction were recorded.

Results

Hypertension as a concomitant illness resulted in significant differences in body mass index (P= 0.045), white blood cells (P=0.003), platelet count (P = 0.011), fasting blood glucose (P= 0.036), serum triglycerides (P= 0.003), and triglyceride- glucose index (P = 0.001).

Conclusion

The pleotropic effects of Dapagliflozin on selected organs and blood cells were affected by concomitant hypertension and its efficacy as an oral antidiabetic agent declined in the presence of high blood pressure but maintained renal function and produced a positive impact on the haematological indices. Additionally, the antihypertensive efficacy of Dapagliflozin decreases as blood glucose and triglycerides increase.

Keywords: *Dapagliflozin, Oral antidiabetic agents, Hypertension, Arterial stiffness index, Myocardial work stress, Triglyceride-glucose index..*

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INTRODUCTION

Dapagliflozin is an oral antidiabetic agent that acts by inhibiting the sodium-glucose co-transporter 2 (SGLT2), leading to a reduction in the renal threshold of glucose reabsorption and thereby glycosuria and lowering of blood glucose levels [1]. Several studies showed that Dapagliflozin is beneficial in treating many pathological conditions that are associated with or complicated by diabetes mellitus (DM) through different mechanisms. A recent meta-analysis study clarified that Gliflozins significantly reduced the metabolic syndrome components, including body weight (BW), waist circumference (WC), blood pressure (BP), and glycol-lipid profile [2]. Dapagliflozin significantly improved the ejection fraction (EF) in healthy subjects and patients with heart failure (HF) [3, 4]. On the blood cells, Dapagliflozin inhibits the activation of the blood platelet, which prevents or reduces the development of thrombosis [5], improves the activity of the neutrophils [6], and increases the haemoglobin (Hb) levels in DM with HF [4]. On renal function, Dapagliflozin non-significantly reduces the estimated glomerular filtration rate (eGFR) in patients with reduced ejection fraction HF [7].

On the other hand, hypertension (HTN) is commonly associated with or is a sequel of type 2 diabetes (T2D), and it has been found that Dapagliflozin is of benefit in reducing systolic pressures [8]. It decreases the reabsorption of glucose in the proximal tubules, causing a reduction in blood glucose levels through an insulin-independent mechanism [9]. It is well known that Dapagliflozin reduces BP in patients with T2D via osmotic diuresis, mild natriuresis, and weight loss [10]. In addition, it has been found that Dapagliflozin reduces serum uric acid levels and will not cause abnormalities in potassium levels [11].

Despite all these known pleiotropic effects of Dapagliflozin, it is not obvious how these effects will appear in the presence or absence of elevated BP and antihypertensive treatments, especially in our society. So, the rationale for this cross-sectional study is that the pleiotropic effects of Dapagliflozin may be well observed in the presence of simultaneous HTN and T2D. This study aimed to test the hypothesis that Dapagliflozin supplementation is of benefit in T2D associated with HTN and concomitant anti-hypertensive treatments compared with T2D without HTN.

MATERIALS AND METHODS

This cross-sectional study was conducted at the University of Sulaimani, College of Pharmacy, Department of Clinical Pharmacy in collaboration with High-Quality Hospitals, Anwar Sheikha Medical City (AMC). The study protocol was approved by the College of Pharmacy's ethics committee (approval number: PH97-23) prior to the recruitment of patient subjects in accordance with the Declaration of Helsinki's ethical principles for human study. Written informed consent was obtained from all the patients at the time of entry into the study. Fifty diabetic patients with/without concomitant HTN who were receiving 10 mg/day of Dapagliflozin plus insulin and/or other oral antidiabetic agents for T2D and attended the endocrinology and internal medicine consultation clinics at AMC were interviewed once to be involved in this study from February to July 2023.

At the beginning of the study, ten patients were excluded because of histories of non-adherence to their medications in the past three months. Later, three more patients were excluded because of invalid blood samples and uncertainties about their medication history. The remaining 37 patients were divided into two groups as follows:

Group I: Consists of fifteen diabetic normotensive patients, five males and ten females, with a median age of 55 (49 – 64) years.

Group II: Consists of twenty-two diabetic hypertensive patients, four males and eighteen females, with a median age of 59 (50.8 – 68.5) years.

The study protocol required patients to be on a stable dose of at least one oral antidiabetic drug and a stable daily dose of insulin for 24 months or longer prior to recruitment. Additionally, Group II patients should receive a stable therapeutic dose of one or more antihypertensive drugs such as angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), calcium entry blockers (CEBs), diuretics or beta-adrenoceptor blockers, prescribed by their specialist doctors, for durations of 12 months or longer. All the studied participants were treated with 10 mg/day of Dapagliflozin at least 12 weeks before being interviewed and involved in this study. No clinical pharmacist interventions and no adjustments to the usual drug regimens or lifestyle of studied patients were permitted in this study. Patients were excluded from the study who had a history of infectious and/or

inflammatory conditions, an eGFR of < 60 mL/min, and patients who were under treatment with corticosteroids or lipid-lowering agents (that may affect the magnitude of pleiotropic effects of Dapagliflozin) or alcoholics.

The body mass index (BMI) was calculated using the equation of the person's weight in kilograms divided by his or her height in meters squared (kg/m2). The BP (mmHg) was measured in the sitting position after 15 minutes of rest three times at the same session for each patient using an electronic sphygmomanometer, and the mean of three readings was taken. Left Ventricular Ejection fraction (LVEF) was measured through transthoracic echocardiography M-mode.

Arterial stiffness index (ASI) and Myocardial work stress (MSW) were calculated using the following equations;

$$\text{ASI} = 1 - \frac{diastolic\ BP}{systolic\ BP} \quad (12)$$

MSW = RPP (beat.min-1. mmHg) = Heart rate × systolic blood pressure × 10-2 (13).

Laboratory investigations

Five milliliters of venous blood were drawn after eight to ten hours of overnight fasting from a large antecubital vein, placed in plain tubes, and sent to the AMC laboratories for analysis. The tests included measurements of haematological indices {Hb, haematocrit, white blood cells (WBC), platelets}, glycaemic indices {fasting blood glucose (FBG), HbA1c}, lipid profile {total cholesterol (T.Chol), serum triglycerides (S.TG)} and renal function {blood urea (BU), serum creatinine (S.Cr)}. eGFR (14) and Triglyceride-glucose index (TyGI) were calculated by using the following equations:

$$\text{Estimated glomerular filtration rate (Cockcroft Gault equation)} = \frac{140 - age\ (year) \times Weight\ (kg) \times 1.23}{Serum\ creatinine\ (\frac{mmoL}{L})}$$ (For women multiply the result of calculation by 0.85)

$$\text{Triglyceride-glucose index (TyGI)} = \text{Ln}\left(\frac{Triglyceride\ x\ glucose}{2}\right)$$

Statistical analysis

The results are expressed as a number, median, and interquartile range. The data were analysed using SPSS -25 (IBM Compatible Corp., Chicago, USA). P-values were calculated to show the differences between Groups I and II using the non-parametric Mann-Whitney test for continuous data, and Fisher's Exact test for categorized data. Boxplots were used to illustrate the differences between the studied groups. A p-value of < 0.05 is a significant cut-off value.

RESULTS

This study includes thirty-seven patients in total, nine (%24) of them were males and twenty-eight (%76) were females, with ages ranging from 49-68.5 years. Fifteen participants had no history of HTN, classified as Group I while twenty-two of them had documented history of HTN and were receiving one or more antihypertensive drugs in the past 12 months or more, categorized as Group II. The patients in Group I suffered from DM for more than 10 years, while the duration of diabetes in Group II was less than 10 years but the difference between them was almost non-significant (P = 0.055).

Table 1 shows the characteristics of the participants who were enrolled in the study. There were no significant differences between Groups I and II in the distribution of sex and residency or the median values of age. The BMI is significantly higher among patients in Group II compared with Group I. Table 2 and Figure 1 show non-significant differences in the median values of mean arterial BP, ASI, and MWS. The echocardiographic study showed a non-significant increase in EF (%) in Group II compared with Group I participants, which amounted to 6.6% of the median value (65 [62.0-65.3]) versus (61 [55-65]). Figure 2 shows a non-significant change in the Hb value, while the WBC and blood platelets were significantly higher by 19.7% (P=0.003) and 23.4% (P=0.011) of the median value, respectively, among participants in Group II compared with Group I, which is also shown in Table 2. Renal function assessed by determination of BU, S.Cr, and eGFR showed non-significant differences in these indices between Groups I and II. The median (interquartile) values of BU, S.Cr, and eGFR in patients of Group II were 29 (24.8-44.8) mg/dL, 0.86 (0.6-0.98) mg/dL, and 84.5 (60.3-134) ml/min versus 35.2 (31.4-37.0) mg/dL, 0.9 (0.84-0.97) mg/dL, and 79 (70-100) ml/min.

The glucometabolic profile showed non-significantly higher fasting T. Chol (170.5 [112.9-187.8]) mg/dL and HbA1c % (8.6 [7.7-10.6]) in Group II compared with

Group I, ((146 [112-161]) mg/dL and (8.3 [7.8-9.6])), respectively. Table 2 and Figure 3 also showed that patients in Group II had significantly higher FBG, fasting serum TG and TyGI which increased by 28.5% (P=0.036), 48.7% (P=0.003), and 7.3% of the median corresponding values in the Group I.

The results are presented as number and median (interquartile). P-value was calculated using Mann-Whitney U test. Group I: Type 2 diabetes without a previoushistoryofhypertension,GroupIIType2diabetes with a previous history of hypertension. A p-value of < 0.05 is considered to be a significant difference. The results are presented as number and median (interquartile). P-value was calculated using Mann-Whitney U test. Group I: Type 2 diabetes without a previous history of hypertension, Group II Type 2 diabetes with a

Table 1. Characteristics of the study participants

Variables	Group I (n=15)	Group II (n=22)	p-value
Sex (Male: Female)	5:10	4: 18	**0.438**
Age (year)	55 (49-64)	59 (50.8-68.5)	**0.400**
Residency (Rural: Urban)	3:12	2:20	**0.377**
Duration of diabetes (year)	10 (10-14)	7.5 (5-12.8)	**0.055**
Body mass index (kg/m2)	25.3 (23.4-28.3)	27.9 (24.7-33.0)	**0.045**

Table 2. Comparison of measured parameters between normotensive and hypertensive diabetic patients receiving 10 mg/day of Dapagliflozin as an oral antidiabetic agent.

Parameters	Group I (n=15)	Group II (n=22)	p-value U-test
Blood pressure (mmHg)			
Systolic	134 (124-156)	154 (130-158)	**0.383**
Diastolic	80 (75-90)	83 (74-91)	**1.000**
Mean	103 (90-112)	105 (96-112)	**0.819**
Arterial stiffness index	0.4 (0.373-0.444)	0.444 (0.394-0.504)	**0.098**
Myocardial works stress	105 (97-134)	129 (107-155)	**0.143**
Ejection fraction (%)	61 (55-65)	65 (62-65.3)	**0.061**
Hematological indices			
Hemoglobin (g/dL)	13.7 (123-14.8)	13.6 (12.8-14.2)	**0.658**
Hematocrirt (%)	41.9 (38-45)	41.3 (39.2-43)	**0.658**
White blood cell (×103/mm3)	7.1 (6.6-7.6)	8.5 (7.9-9.1)	**0.003**
Platelet count (×103/mm3)	231.3 (188-250)	285.5 (262.3-317.3)	**0.011**
Glycemic indices			
Fasting blood glucose (mg/dL)	144 (115-194)	185 (138-209)	**0.036**
Glycosylated hemoglobin (%)	8.3 (7.8-9.6)	8.6 (7.7-10.6)	**0.614**
Lipid profile (mg/dL)			
Total Cholesterol	146 (112-161)	170.5 (112.9-187.8)	**0.334**
Serum Triglycerides	118 (99.5-152.0)	175.5 (138-239.5)	**0.003**
Triglyceride-glucose index	9.02 (8.78-9.43)	9.68 (9.27-10.28)	**0.001**
Renal function			
Blood urea (mg/dL)	35.2 (31.4-37.0)	29 (24.8-44.8)	**0.614**
Serum creatinine	0.9 (0.84-0.97)	0.86 (0.6-0.98)	**0.572**
Estimated glomerular filtration rate (mL/min)	79 (70-100)	84.5 (60.3-134)	**0.915**

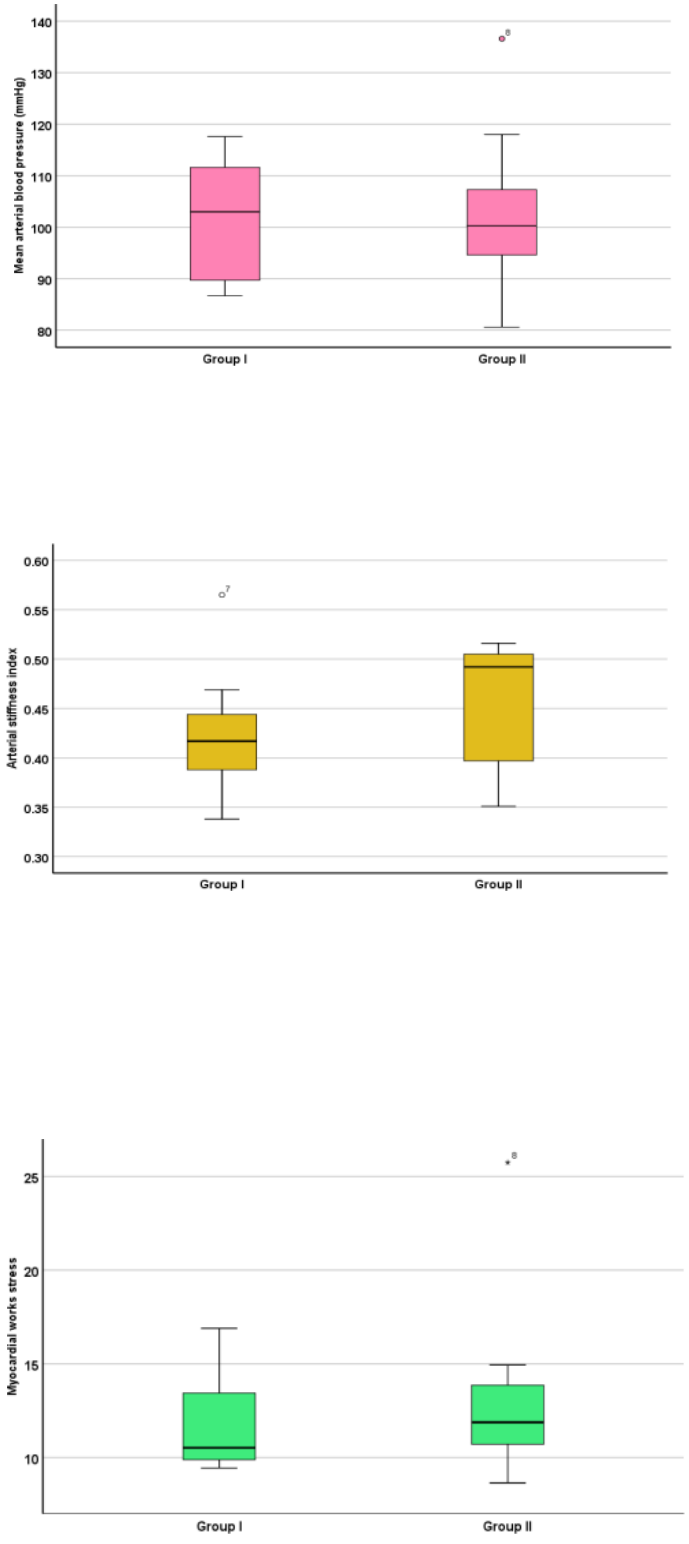
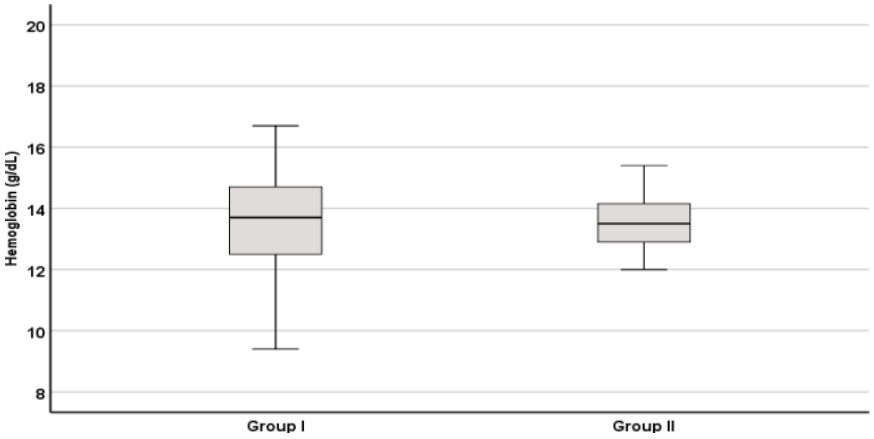
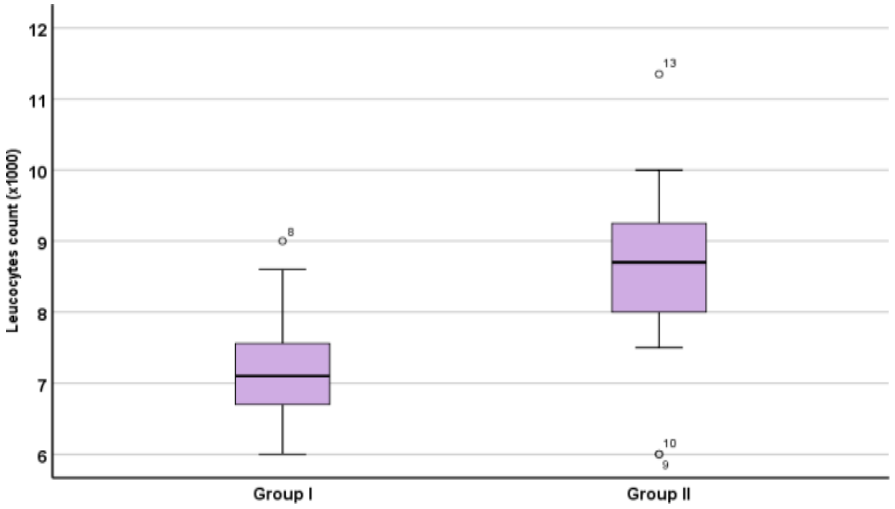
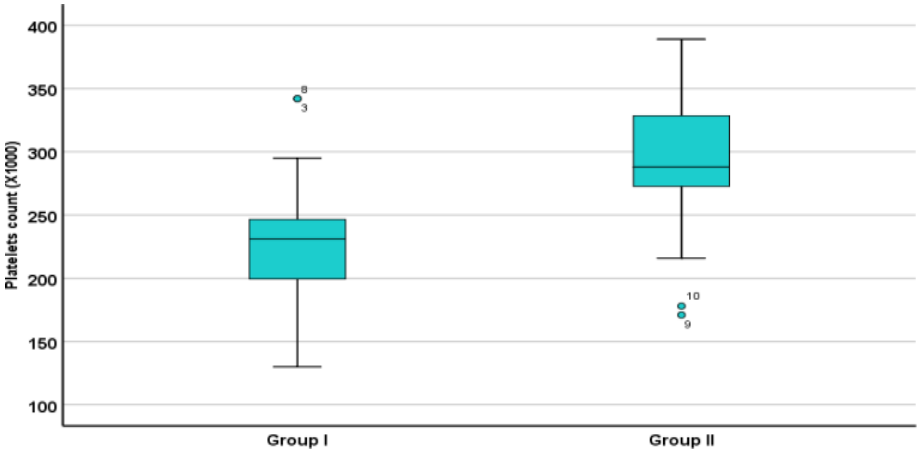


Figure 1. Boxplot shows non-significant differences between Group I and Group II in mean arterial blood pressure (upper), arterial stiffness index (middle) and myocardial works stress (lower).


Hemoglobin (g/dL)
20
18
16
14
12
10
8
Group I
Group II


Leucocytes count (x1000)
12
11
10
9
8
7
6
13
8
10
9
Group I
Group II


Platelets count (X1000)
400
350
300
250
200
150
100
8
3
10
9
Group I
Group II

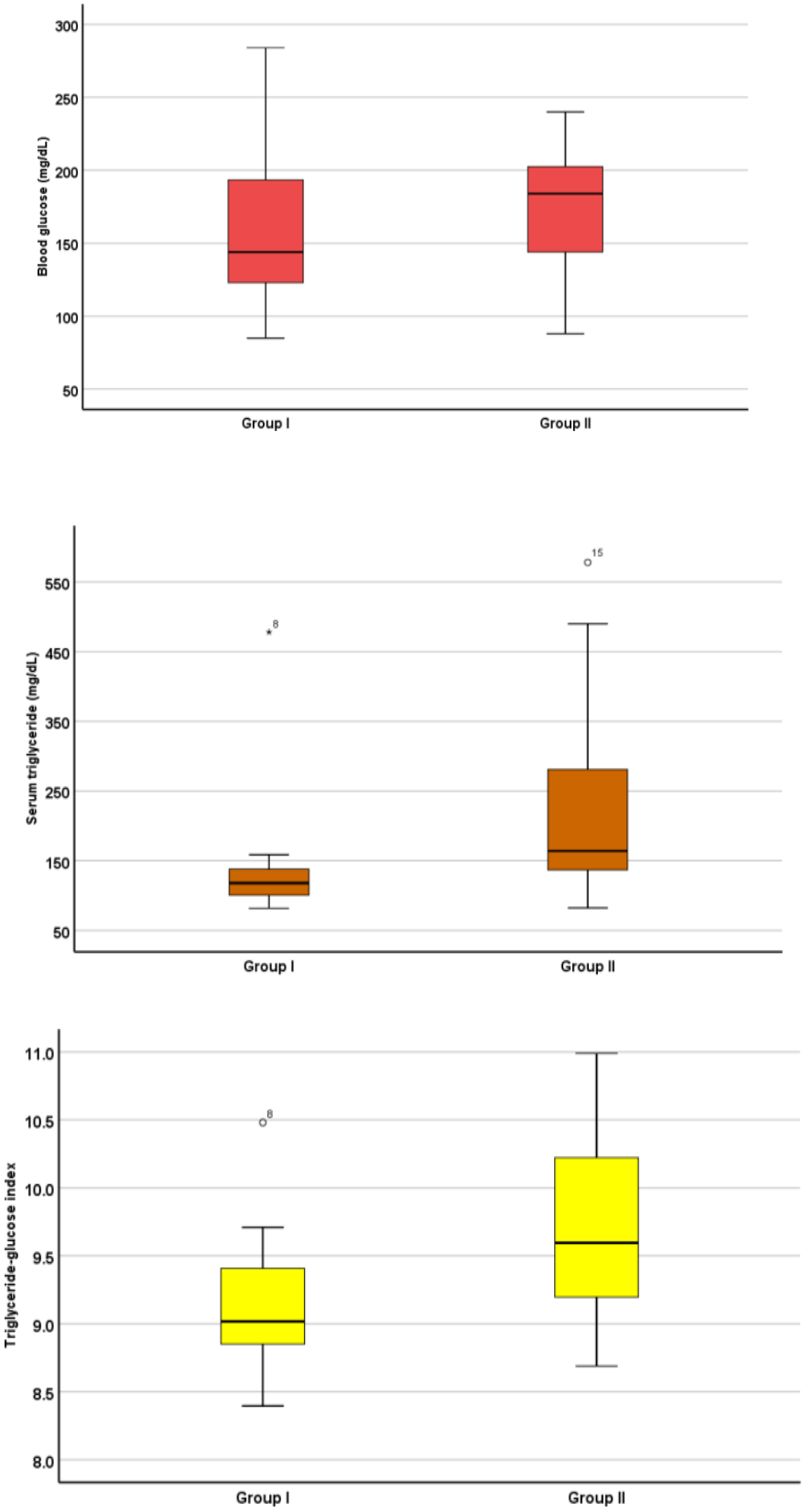


Figure 2. Boxplot of haematological indices shows non-significant changes in haemoglobin level (upper), significant higher levels of leucocytes (p=0.003, middle) and blood platelets (p=0.011, lower) among participants of Group II compared with Group I

DISCUSSION

The current cross-sectional study was designed to examine the difference in effects of Dapagliflozin in diabetic patients with and without HTN who are receiving insulin plus one or more oral antidiabetic agents with no changes in the usual dose or additions of other supplementary agents for the study.

Inhibitors of SGLT2 constitute a relatively novel class of oral antidiabetic agents that have gained a lot of attention in the past decade due to their insulin-independent mechanism of action and effectiveness in reducing body weight and blood glucose levels [(15)]. It is well known that SGLT2 inhibitors can have effects beyond enhancing urinary glucose excretion, extending to improvements in cardiovascular disease-related mortality, BP [(16)], liver steatosis [(17)], and visceral fat mass [(18)]. Despite all of these facts, there are uncertainties about the influence of existing diabetes complications such as HTN, on the effects of SGLT2 inhibitors on various organ functions.

In the present study, the BMI of diabetic normotensive patients was significantly lower compared to those with elevated BP (25.3 vs 27.9, P = 0.045) although the duration of diabetes was longer in the normotensive patients' group and this difference was almost significant (P = 0.055). This indicates that HTN and elevated BP were associated with higher BMI and obesity, a finding that may be explained by the possibility that these patients were not compliant with their medications or did not follow active lifestyle and dietary recommendations for preventing disease progression until complications appeared. The net result of this non-adherence is rationally the attenuation of the weight-loss effect of Dapagliflozin in patients with diabetes complications. In a study done by Calapkulu et al. [(19)], researchers found that Dapagliflozin can reduce body weight and BMI by 5% in six months. This may be related to the fact that Dapagliflozin is usually started in diabetic patients who are overweight and not responsive to insulin and/ or other oral antidiabetic agents because of its effect in helping to lose calories by increasing urinary glucose excretion, which helps to lose weight, an effect that seems to be altered in the presence of HTN. On the other hand, results of statistical analyses revealed that age, gender, duration of illness, or history of HTN did not have a significant effect on anthropometric changes (19) including BMI, findings that are compatible with the present study except for history of HTN, which appears to have roles in the attenuating SGLT2 weight-loss effect.

Linear proportional control of BP with blood glucose is a very important factor for reductions in cardiovascular risks because HTN is known to be one of the common complications of T2D [(20)] and diabetes itself confers an independent cardiovascular risk [(21).] In this study, all the measured parameters related to cardiovascular systems risk assessment, such as SBP, DBP, MAP, ASI, MSI, and serum T.Chol readings, were higher in Group II patients than in Group I, but the difference was statistically non-significant. Other parameters such as serum TG and TyGI were significantly higher in Group II patients than in Group I (P = 0.03 and 0.01, respectively). The fact that the antihypertensive and cardio-protective effects of Dapagliflozin may be abolished in diabetic hypertensive patients who also receive a thiazide diuretic and hence result in a smaller reduction in body weight [(20)] may confirm a lesser diuretic action of Dapagliflozin in these thiazide-treated patients since most of the patients in Group II were receiving a daily morning dose of thiazide diuretics for synergistic BP control. A study done by Weber et al. [(22)] did not observe a significant reduction in DBP with Dapagliflozin, while another study by Han et al [(23)] reported that, although the BP in studied samples was in the recommended cut-off range for diabetes patients at baseline, gradual significant declines in both SBP and DBP were observed during Dapagliflozin treatment. Additionally, it was found that Dapagliflozin causes greater reductions in BP in hypertensive patients than in normotensive subjects [(24).] This effect begins to be noticed in the first week of starting treatment and may be maintained for many years [(24)] a result that has been supported by real-life observational studies [(25, 26)] which does not seem to be the case in this study.

Insulin resistance and uncontrolled blood glucose have been shown to increase the risks of the development of arterial wall atherosclerosis, thus increasing arterial stiffness [(27)] but the presence of HTN and poor glycaemic control seems to have no influence on the effects of Dapagliflozin on arterial stiffness because in the present study, both groups reported the same ASI and they were non-significantly different (P = 0.098), which means that coexisting HTN as one of the main diabetic complications has no effect on ASI even in cases of significantly uncontrolled blood glucose levels.

Although the estimation of MWS is not an accurate and specific method for measuring cardiovascular risk, several studies have reported its validation in

estimating workload on the heart [28]. In the present study, Group II patients showed higher MWS compared to Group I (129 versus 105) but the difference was non-significant (P=0.143). This means that Dapagliflozin in the presence of elevated BP may lose cardioprotective properties supported by a significant increase in platelet count, WBCs, and TyGI indicating risks of atherogenesis and inflammatory processes.

The ability to regulate lipid synthesis, transport, and oxidation-associated molecules has allowed SGLT2 inhibitors to produce effects extending to lipid metabolism and processing inside the body [29]. Modest reductions in serum TG levels after initiating treatments with Dapagliflozin and increases in both T.Chol and HDL-C were reported in many studies [30, 31]. Additionally, other studies with smaller sample sizes showed no changes in the lipid profile of the studied subjects after Dapagliflozin treatment [32]. Other markers for assessing cardiovascular risk such as TyGI and atherogenic index, were described as decreasing in diabetic patients receiving Dapagliflozin treatment [33].

As a result of its long-standing good reputation in cardiology, LVEF is still the most widely used parameter of systolic function [34] and is widely used in real-life experiments to monitor the effect of medications on cardiovascular outcomes. Improvements in LVEF and reductions in hospitalization rates, even in patients without concomitant HF, have been found to be evident in T2D patients receiving Dapagliflozin or other SGLT2 inhibitors in many real-life studies [35, 36].

Although the result was non-significant (P =0.061), echocardiography showed that Group II patients have a higher EF than Group I patients. This illustrates that Dapagliflozin preserves EF more when complications such as HTN exist. Ultimately, despite the non-significant differences in BP readings between the two studied groups, this study was not designed to specifically measure and monitor the co-existing major cardiovascular endpoints.

Heyman et al [37] concluded that the use of SGLT2 inhibitors is associated with an increase in hematocrit by an unknown mechanism. On the contrary, Ghanim et al [38] reported that there is only a preliminary transient contraction in the plasma volume after these drugs induced glycosuria and, hence, it does not explain the persistent increase in hematocrit. Furthermore, a research has postulated that increments in hematocrit may be related to increases in oxygen-carrying capacity by SGLT2 inhibitors, leading to beneficial cardio-protective effects [39]. In Ghanim et al [38] study, there was also a significant increase in Hb concentration in patients who received Dapagliflozin. In the present study, haematological indices such as haematocrit and Hb were nearly the same in both groups, and only WBC and platelet counts were significantly higher in Group II patients (P = 0.003 and 0.011 respectively). This may be explained by the fact that Dapagliflozin in diabetic patients with HTN has no beneficial effects on Hb and haematocrit and again, HTN attenuates its cardio-protective effect through a yet different mechanism. Significantly higher levels of WBC and blood platelets in the presence of elevated BP, indicates an ongoing inflammatory process and risks of atherogenesis that may increase risks of cardiovascular events.

Controversy exists about the results of many studies that reported an association of a subclinical inflammatory marker (WBC) with T2D and insulin resistance [40]. It was found that poorly controlled diabetes causes augmented platelet-dependent thrombin generation, platelet activation, and higher plasma levels of coagulation markers which are known to be crucial factors for initiating atherogenesis and atheroprogression [41] causing deleterious cardiovascular effects like myocardial infarction (MI) and HF, which appear to be magnified in the presence of concomitant HTN. Glezeva et al [42] found that attenuated platelet activation, a dimension of atherosclerosis, favorably influences plaque composition and blood lipid profile. Activated platelets facilitate leucocyte adhesion to the endothelium and subsequent immune cell recruitment to the vascular wall. It is notable that platelet–leucocyte aggregates have been identified as important factors driving not only atherothrombosis and atherosclerosis but also myocardial dysfunction and HF. Ultimately, Dapagliflozin induced reductions in platelet–leucocyte aggregates can confirm the hypothesis of reduced atherogenesis due to less platelet-mediated inflammation and implicate a clinical impact on cardiovascular events [43], an effect that appears to be lost in diabetes hypertensive patients.

Other parameters such as FBS and HbA1c were higher in Group II patients than Group I with FBG levels significantly higher (P =0.036) in hypertensive patients which may be related to the non-adherence of these patients to a healthy lifestyle which is evident by the high level of HbA1c in both groups, indicating poor glycemic control in the past three months, with levels higher in hypertensive patients. It is worth mentioning

a study by Kim et al (44) that found that Dapagliflozin had no effect on FBG, insulin, or HbA1C levels. The interesting result was that the renal function tests such as BU and S.Cr were reduced in hypertensive patients and eGFR increased, although the difference was non-significant. This may indicate that Dapagliflozin may confer more renal protection when HTN exists as a complication of diabetes although previously it was found that Dapagliflozin can produce a maximal beneficial effect in patients with an early stage of DM and renal hyperfiltration [(23)].

CONCLUSIONS

The efficacy of Dapagliflozin as an oral antidiabetic agent declines in the presence of high BP. HTN as a complication of diabetes causes attenuation of Dapagliflozin's weight losing capacity and cardio-protective effects through significant effects on WBC, platelets, TyGI, serum TG and FBG. Dapagliflozin can non-significantly improve and preserve the EF and renal function in hypertensive patients. On the other hand, the efficacy of Dapagliflozin is decreased as the FBG and TG increase, and it shows pleiotropic effects (maintaining renal function and positive impact on the haematological indices) whenever there are complications like HTN, and dyslipidaemia.

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