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Marwan S. Al-Nimer[1], Ismail Ibrahim Latif[2], Thaqeef Murtada Jawad[3]
[1]Department of Clinical Pharmacology and Therapeutics, College of Diyala, University of Diyala, Baqubah, Iraq
[2]College of Medicine, University of Diyala, Baqubah, Iraq
[3]College of Science, University of Wasit, Wasit, Iraq

Effects of Sitagliptin versus Empagliflozin on the Stress Hyperglycemic Ratio in People with Type 2 Diabetes: An Open-Label, Randomized Controlled Trial

ABSTRACT

Objective: Stress hyperglycemia (SH) is simply assessed by calculating the stress hyperglycemia ratio (SHR). This study aimed to calculate the SHR in type 2 diabetes (T2D) patients receiving oral diabetes medications that worked through two different mechanisms.

Materials and methods: This open-label randomized clinical trial was conducted in the College of Medicine, University of Diyala, Baqubah, Iraq, from January 1, 2022, to December 31, 2022. Patients with T2D without a previous history of surgical procedures and with no acute or chronic infections were randomly assigned to receive sitagliptin/metformin 50/500 mg or empagliflozin/metformin 10/500 mg orally once daily. Patients were randomized in-hospital, and treated for up to 10 weeks. The primary outcome of this open-label clinical trial was SH, defined as the estimated plasma glucose, and SHR values. The secondary outcome included hematological indices and C-reactive protein (CRP).

Results: Eighty patients with T2D were enrolled in the study and divided into two groups. Group I (n = 40) received sitagliptin/metformin, and Group II (n = 40) received empagliflozin/metformin. The baseline data showed non-significant difference between the two groups in the SH and SHR. The median values of SHR decreased by 9.2% (0.925 vs. 0.840, p = 0.047) in Group I compared with an 8.7% decrease (0.940 vs. 0.858, p = 0.113) in Group II patients. The median values of CRP were non-significantly decreased in Group I (6.0 vs. 5.3 mg/dL, p = 0.507) and remained unchanged in Group II (3.4 vs. 3.4 mg/dL, p = 0.769).

Conclusions: Sitagliptin has a better effect against stress hyperglycemia ratio than empagliflozin. (Clin Diabetol 2024; 13, 3: 156–163)

This study was registered on ClinicalTrial.gov (NCT 05822674)

Keywords: type 2 diabetes, stress hyperglycemia, sitagliptin, empagliflozin

Introduction

Stress hyperglycemia (SH) is an increase in circulating glucose levels in biological fluids as a physiological response to stress in patients with established or newly diagnosed diabetes, or a pathological condition associated with in-hospital-related hyperglyce-

Address for correspondence:
Marwan S. Al-Nimer
Department of Clinical Pharmacology and Therapeutics,
College of Diyala, University of Diyala, 32001 Baqubah, Iraq
E-mail: alnimermarwan@ymail.com
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mia [1–3]. It is also known as transient hyperglycemia during the course of diabetes, and it is thought to be a predictor of increased morbidity and mortality [4]. Stress hyperglycemia has been found to be a short- and long-term prognostic marker for complicated or associated diabetes mellitus. In a cohort study that included 3636 patients admitted to the intensive care unit, it was found that the stress hyperglycemia ratio (SHR) is associated with mortality in patients with critical illnesses, and a higher mortality rate was observed in non-diabetic patients [5]. In another study, the cutoff point of SHR for poor prognosis in patients with acute coronary syndrome, who were followed up for two years, was 0.78 [6]. In a retrospective study that included 599 patients with acute heart failure, the risk of mortality was associated with a low SHR of 0.88 in diabetes, while such an association was not observed in non-diabetes [7]. Therefore, the SHR was linked with a poor prognosis in patients who were critically ill, irrespective of whether they were subjected to the stress of the surgical procedures. In in-hospital patients with diabetes and heart failure, both low and high ratios of SHR were associated with unfavorable outcome events [8]. Glycated hemoglobin (HbA1c) is a measure of average blood glucose levels over the last 2–3 months and is not affected by transient hyperglycemia [9, 10]. The SHR is a proposed measure of SH that can be calculated by dividing the blood glucose on admission (current) (mmol/L) by the HbA1c value [11]. Others calculated the SHR by dividing the admission (current) blood glucose level by the estimated average glucose level over the preceding 2–3 months, according to the following formula: ([1.59 × HbA1c current value] – 2.59) [12, 13]. Through their pleiotropic effects, some oral hypoglycemic agents improve SH. When compared to non-SGLTi (sodium glucose transporter inhibitor) users, patients with diabetes who used SGLTi and had an acute myocardial infarction had less prevalent SH, a smaller infarct size, and evidence of a low inflammatory response [14]. Empagliflozin has been approved for the treatment of diabetes and symptomatic heart failure with preserved and reduced ejection fraction, and it significantly reduces the mortality rate in hospitalized chronic heart failure patients [15]. Empagliflozin provides a good prognosis for diabetes treatment outcomes, which is due to improvement in related risk factors for cardiovascular events [16]. In addition, it showed an anti-inflammatory effect that is mediated by attenuating the formation of inflammatory cytokines [16]. Another double-blind randomized clinical trial reported that pre-operative sitagliptin (a dipeptidyl peptidase-4 inhibitor) did not prevent SH in patients with diabetes undergoing general surgery [17]. Another study found that sitagliptin did not prevent acute hyperglycemia in patients without diabetes undergoing coronary artery bypass graft surgery [18].

The rationale for this study is that oral hypoglycemic agents may potentially overcome the stress-induced hyperglycemia to a certain extent. The aim of this observational clinical study was to assess SHR in type 2 diabetes (T2D) patients without other serious diseases who used fixed dose combinations of sitagliptin/metformin compared with those who used empagliflozin/metformin.

Materials and methods

Study design

This open-labeled randomized clinical trial included consecutive patients between January 1 and December 31, 2022 from the consultant clinics at the diabetes center and the public clinic database.

Study participants

The patients who were treated with oral antidiabetics (either sitagliptin/metformin or empagliflozin/metformin) were allocated randomly between two treatment groups using 1:1 allocation system (Fig. 1).

The inclusion criteria for the patients included: (i) patients aged 35 to 70 years; (ii) patients with the duration of diabetes of 1–8 years; (iii) patients treated with oral hypoglycemic agents in form of a combination of sitagliptin/metformin or empagliflozin/metformin. Exclusion criteria included: (i) serious illnesses or surgical interventions within 3 months; (ii) anemia; (iii) patients with chronic inflammatory or autoimmune diseases; (iv) treatment with corticosteroids or non-steroidal anti-inflammatory drugs; (v) pregnancy and nursing mothers. Ultimately, 80 participants with T2D were enrolled. Then, patients were divided according to their pharmacotherapy based on the use of oral hypoglycemic agents into Group I (n = 40): patients treated with sitagliptin/metformin (50 mg/500 mg) and Group II (n = 40): patients who were treated with empagliflozin/metformin (10 mg/500 mg). The duration of each treatment was 10 weeks.

Ethical approval

This study was approved by the Medical Ethics Committee of the College of Medicine at the University of Diyala in Iraq (No. MSM735, date 01-03-2023) and registered on ClinicalTrial.gov (NCT 05822674). Given the patient follow-up nature of this study, informed consent from each patient was obtained. The study protocol was conducted according to the ethical guidelines of the Declaration of Helsinki.

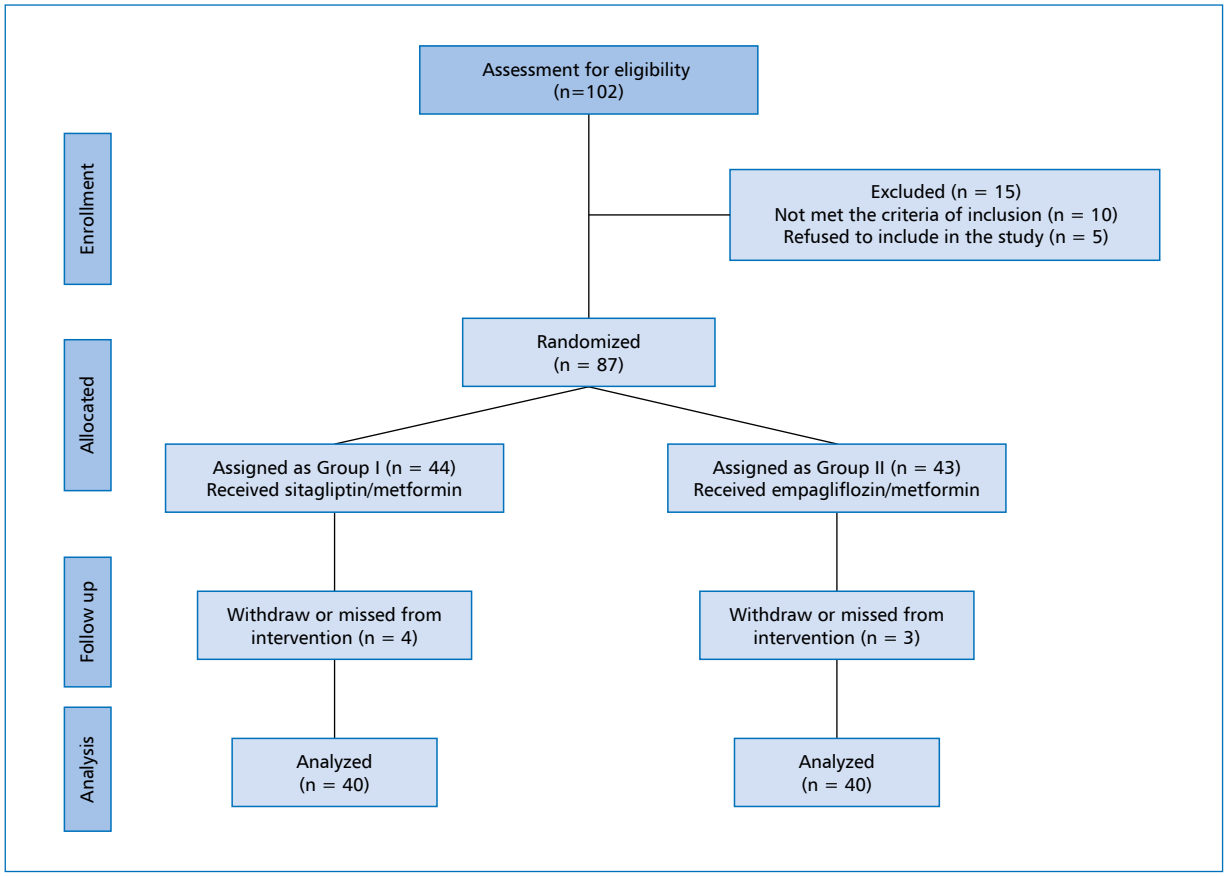

Figure 1. Flowchart of the Participants Included in the Study

Data collection

The medical records of patients attending the clinics were reviewed. Patient characteristic including age, gender, duration of diabetes, history of surgical interventions, and hospital admissions were collected. Laboratory tests [fasting plasma glucose levels (FPG), HbA1c%, hemoglobin (Hb), mean corpuscular volume of red blood cell (MCV), and C-reactive protein (CRP) were carried out at the time of attending the clinics. The laboratory data were collected at the initiation of pharmacotherapy and at the end of 10 weeks of treatment.

Assessment of stress hyperglycemia

Blood samples were drawn in the morning after an overnight fast (at least 8 h) to measure fasting plasma glucose (FPG), HbA1c%, and hematological indices (Hb and MCV). Each blood sample was divided into two portions; the first portion was drawn into an EDTA-test tube, and the second portion was drawn into a plain test tube. Then the samples were centrifuged at 3000 rpm for 15 minutes. The Cobas C311 analyzer (Roche, Germany) was used for the determination of FPG, HbA1c%, and CRP coefficients of variation ranged between 1.8 and 2.3%). The hematological indices were determined by an automatic Coulter analyzer. SHR was calculated according to the following formula: current FPG (measured during a clinic visit) / FBS estimated, the estimated FPG was calculated by sing the formula: 28.7 × current HbA1c % (measured during a clinic visit) minus 46.7 [13, 19].

Statistical analysis

The results are presented as number, percentage, median, interquartile range, and 95% confidence interval (CI). The sample size for the participants was estimated using the GPower software version 3.1 (software developed by Heinrich-Heine-Universität Düsseldorf, Germany, which is free to download for both Windows and Mac OS X platforms), with power (1-error) set at 0.80 and error (α) set at 0.05. The principle of this program is to obtain the sample size, the critical t-value, and the actual power by selecting the appropriate statistical text and the types of power analysis, then feeding the input parameters, which included two tails, alpha error (0.05), and the power (1-beta power of 0.8). The sample size was computed and found to

be 40 participants for each group. The analysis of the data using Shapiro Wilk test showed that the data were not normally distributed. The results were analyzed by Mann Whitney U-test for the effects of each drug on the variables and comparison between two groups, and Chi-squared test for categorical data. Pearson's (rho) correlation between SHR and CRP was computed to show the association between SHR and the inflammatory biomarker. All statistical analysis and boxplot graphs were carried out using SPSS version 24 (IBM Corp., Chicago, USA). A p-value of less than 0.05 is considered significant.

Results

Table 1 shows a non-significant difference in the baseline characteristics, including age, sex, and glycemic indices, between Groups I and II. A significantly higher median value of MCV was observed in Group I, while the Hb and CRP levels were not significantly different between Groups I and II. Table 2 shows sitagliptin/metformin treatment significantly reduced the glycemic indices measured on visiting (current), and attended 22.7% (FPG) and 14.6% (HbA1c%) after ten weeks of treatment. The estimated FPG was significantly decreased by 17.9%, which is less than the reduction in this percentage of median value on visiting (current). The median value of SHR was significantly decreased by 9.2% (Tab. 2 and Fig. 2). These changes were accompanied by a significant ($p = 0.006$) decrease in the Hb level (6%), and non-significantly reduction in the MCV (0.7%) and CRP (11.7%) median values. Comparable effects were observed in Group II as FPG and HbA1c % were decreased by 40.7% and 26.1%, respectively (Tab. 2). The estimated FPG was significantly decreased by 31.7%, which is higher than the corresponding value in Group I. The changes in the SHR were non-significant (decrease by 7.4%) (Tab. 2 and Fig. 2). The median values of Hb, MCV, and CRP were non-significantly changed. The baseline (current values) correlation between SHR and CRP values was non-significant ($r = 0.099$, df: 78, $p = 0.382$). The number of participants with a SHR value more than one, and treated with empagliflozin-metformin (Group II), was significantly decreased from 16 to 7 patients ($p = 0.026$), but those treated with sitagliptin-metformin (Group I) were not significantly decreased from 12 to 8 patients ($p = 0.301$).

Discussion

The results of this study show that oral hypoglycemic drugs have variable effects on the estimated FPG and SHR by reducing the magnitude or the number of the participants who had an SHR value of more than one, in absence stress by the evidence of a non-significant correlation between SHR and CRP. There is no significant difference in the baseline characteristics between Groups I and II except for the MCV, which is within the normal range. Sitagliptin significantly reduced the current FPG values and estimated (stress) median values by 22.7% and 17.9%, respectively, indicating that sitagliptin is effective in reducing stress hyperglycemia. This effect supported a previous study, which showed that sitagliptin supplementation to burned patients significantly attenuated the stress hyperglycemia and reduced the insulin requirements [20]. On the other hand, sitagliptin does not prevent stress hyperglycemia in patients without diabetes who were subjected to open cardiac surgery as it did not reduce

Table 1. The Characteristics Baseline Data of the Participants

Characteristics	Group I (n = 40)	Group II (n = 40)	p-value
Age [year]	47.5 (42.3–53.8)	46.0 (39–52)	0.090
Sex (female:male)	30:10	22:18	0.060
Duration of diabetes [year]	4.0 (2.0–5.0)	3.0 (2.0–4.0)	0.453
Fasting plasma glucose [mg/dL]	185.0 (162.5–238.0)	216.0 (177.0–302.0)	0.235
HbA1c%	8.9 (8.4–10.0)	9.2 (8.4–10.3)	0.855
Hemoglobin [g/dL]	13.4 (12.6–15.2)	14.2 (12.7–15.1)	0.331
Mean corpuscular volume [fL]	88.2 (84.6–90.8)	84.9 (79.6–87.9)	0.006
C-reactive protein [mg/L]	6.0 (1.9–11.3)	3.4 (2.1–8.6)	0.167

The results are expressed as number and median (25th–75th percentiles); p-value was calculated by non-parametric (Mann-Whitney U) test and Chi-square test; Group I: sitagliptin/metformin-treated group, and Group II: empagliflozin/metformin-treated group

HbA1c — glycated hemoglobin

Table 2. Comparison between the Effects of Sitagliptin/Metformin and Empagliflozin/Metformin on the Glycemic, Hematological, and Inflammatory Indice

Variables	Group I (n = 40)					Group II (n = 40)				
	Before treatment		After treatment		p-value	Before treatment		After treatment		p-value
	Median (interquartile range)	95% CI	Median (interquartile range)	95% CI		Median (interquartile range)	95% CI	Median (interquartile range)	95% CI	
Stress hyperglycemia ratio	0.925 (0.17)	0.866–1.018	0.840 (0.15)	0.836–0.939	0.047	0.940 (0.41)	0.939–1.139	0.870 (0.15)	0.858–0.997	0.113
Estimated FPG (mg/dL)	208.7 (44.5)	208.1–227.3	171.4 (27.3)	166.3–168.9	<0.001	217.3 (53.8)	207.9–228.4	148.5 (35.9)	148.9–164.1	< 0.001
Current FPG (mg/dL)	185.0 (75)	183.7–231	143.0 (43.8)	142.1–172.9	<0.001	216.0 (125.0)	204–244.6	128.0 (38.5)	131.1–160.8	< 0.001
Current HbA1c %	8.9 (1.6)	8.9–9.5	7.6 (0.95)	7.4–8.1	<0.001	9.2 (1.9)	8.9–9.6	6.8 (1.3)	6.8–7.3	< 0.001
Hemoglobin (g/dL)	13.4 (2.6)	13.2–14.2	12.6 (2.5)	12.2–13.3	0.006	14.2 (2.4)	13.3–14.5	13.7 (1.5)	12.9–13.9	0.142
Mean corpuscular volume (fL)	88.2 (6.1)	85.0–89.0	87.6 (4.4)	84.1–88.2	0.389	84.9 (8.3)	78.7–85.0	81.8 (16.0)	75.9–82.5	0.184
C-reactive protein (mg/L)	6.0 (9.5)	6.2–11.9	5.3 (5.3)	5.1–8.2	0.507	3.4 (6.5)	4.2–8.1	3.4 (6.0)	3.8–7.5	0.769

The results are presented as a median (interquartile range), and 95% confidence interval (CI); p-values were calculated by non-parametric (Mann-Whitney U) test;
Group I: sitagliptin/metformin-treated group, and Group II: empagliflozin/metformin-treated group

FPG — fasting plasma glucose; HbA1c — glycated hemoglobin

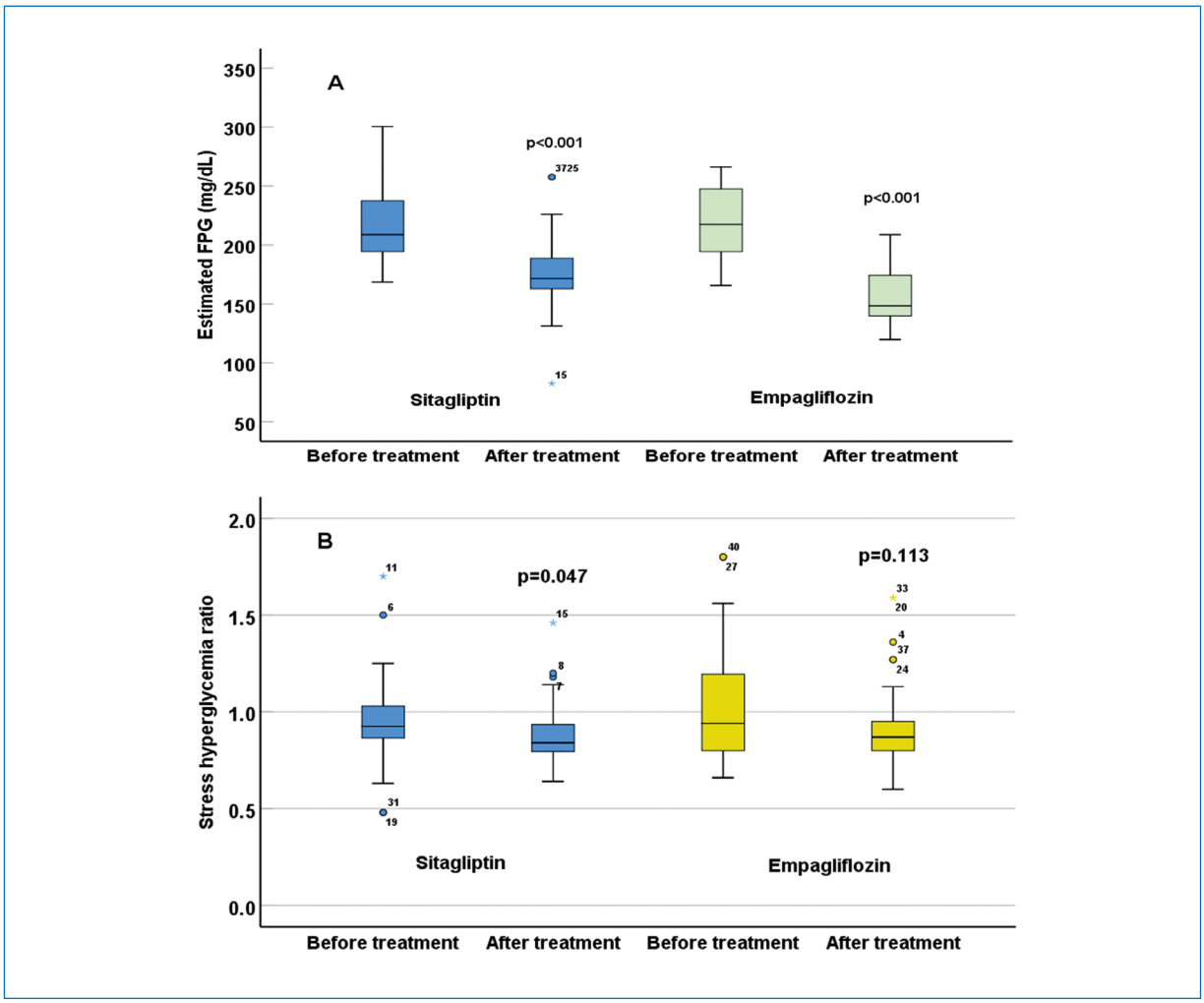

Figure 2. Effects of Sitagliptin and Empagliflozin **A.** on the Estimated (Stress) Fasting Plasma Glucose (FPG) Level and **B.** on the Stress Hyperglycemia Ratio
p-values compared with the corresponding before-treatment level of each intervention

the frequency of stress hyperglycemia [18]. Therefore, sitagliptin could be useful to combat stress hyperglycemia in the presence of inflammation, as sitagliptin has anti-inflammatory property [21]. In this study, sitagliptin reduced CRP levels from a median value of 6 mg/L to 5.3 mg/L, which supports previous studies that sitagliptin suppressed diabetes-related inflammation [22]. These observations explained the results of our study which found that sitagliptin significantly decreased the SHR value but not the frequency of participants with SHR value of > 1 as a marker of stress hyperglycemia. Hemoglobin level was significantly decreased in sitagliptin-metformin group from a median value of 13.4 g/dL to 12.6 g/dL. This effect may be due a rare side effect of sitagliptin, which can cause red blood cell hemolysis, or metformin, which rarely causes megaloblastic anemia due to vitamin B12 deficiency [23, 24]. Empagliflozin-metformin significantly reduced the FPG (current and estimated values), and glycated hemoglobin, but it did not significantly reduce the median SHR value. It significantly decreased the frequency of participants who had an SHR value of > 1. These results confirmed a previous experimental study, which showed that empagliflozin reduced stress-induced hyperglycemia in certain number of mice, and it cannot protect the brain from the effect of hyperglycemia on memory [25]. In another experimental animal study, empagliflozin attenuated the late sequalae of acute hyperglycemia associated with acute myocardial infarction by reducing the cardiac tissue fibrosis [26]. Non-significant effects of empagliflozin on the red blood cell indices confirmed a previous study, which showed that empagliflozin has positive effect on hemoglobin by reducing the new-onset anemia, and its pleotropic effects are not affected by the presence of anemia [27]. Empagliflozin in a dose higher than that

used in this study (25 mg vs. 10 mg, daily) suppresses the inflammatory biomarkers, which explained our results that empagliflozin had no significant effect on the median value of CRP [28]. This study indicates that the pleiotropic effects of sitagliptin and empagliflozin have a role in decreasing the SHR value. Among these pleiotropic effects are cardioprotection with empagliflozin and the anti-inflammatory effect with sitagliptin [29, 30]. Patients with diabetes are at risk for developing acute coronary syndrome, heart failure, autonomic cardiac neuropathy, etc., which are categorized as life-threatening conditions [31]. Therefore, the determination of the SHR value as a prognostic biomarker will be helpful in those patients who were treated with empagliflozin. On the other hand, the comorbidities of diabetes indicate that inflammation is a predisposing etiopathological factor, as with diabetic foot, peripheral neuropathies, etc. [32]. The determination of SHR could be useful in the assessment of sitagliptin in these pathological conditions. Therefore, the application of SHR is not solely related to the stress that results from surgical interventions or septicemia, but it can be extended to the assessment of diabetic co-morbidities as well as the pleiotropic effects of oral antidiabetic agents. The strength of this study is the demonstration of a significant effects of oral hypoglycemic agents on SHR, that characterized by a reduction in the SHR level (to less than 1) and the frequency of patients with SHR of > 1. Another important point is that determining the SHR value helps the clinician in controlling diabetes. Limitations of the study include small sample size and inclusion of only two red blood cell indices. Further investigation into the application of SHR as a predictive biomarker in empagliflozin-treated chronic heart failure with or without diabetes could be a valuable strategy because cardiovascular events are potentially critical illnesses associated with the risk of poor outcome.

Conclusions

Both sitagliptin and empagliflozin reduced the magnitude of the median value of SHR from 0.925 to 0.840 (9.2%) with sitagliptin treatment, and the frequency of patients with SHR > 1 from 16 to 7 patients (43.8%) with empagliflozin treatment. Sitagliptin significantly suppressed the inflammatory marker and reduced the hemoglobin levels. Therefore, SHR value could help the clinicians to monitor diabetes control. This study leads us to identify the SHR cutoff value as a short- and long-term prognostic biomarker in the management of hospitalized patients with diabetes and concomitant cardiovascular diseases or neuropathies, as these comorbidities are associated with inflammation and poor prognosis.

Article information

Data availability statement

The data is available upon request with permission from the corresponding author.

Ethics statement

This study was approved by the Medical Ethics Committee of the College of Medicine at the University of Diyala in Iraq (No. MSM735, date 01-03-2023) and registered on ClinicalTrial.gov (NCT 05822674). Given the patient follow-up principle of this study, informed consent from each patient was obtained. The study protocol was conducted according to the ethical guidelines of the Declaration of Helsinki.

Authors contribution

MSAl-N conceived and designed the study, collected the data, performed the statistical analysis, and wrote the first draft. IIL: collecting and interpreting the data. TNJ: collecting, performing the statistical analysis, and interpreting the data. All authors reviewed and edited the manuscript and approved the submission.

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Conflict of interest

The authors declare no conflicts of interest.

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