A comparative study of the cardioprotective effect of Metformin, Sitagliptin and Dapagliflozin on Isoprenaline induced myocardial infarction in non-diabetic rats

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Abstract

Background: Acute myocardial infraction (AMI) is a leading cause of morbidity. As anti-diabetic drugs affect the cardiovascular risk of diabetic patients independent of their glucose lowering effect, this study was aimed to explore the cardioprotective effects of metformin, sitagliptin and dapagliflozin on electrocardiogram (ECG) changes, IL-1β, troponin I, caspase 3 in isoprenaline (ISO) induced MI in non-diabetic rats. The present study was conducted on 40 adult male Wistar albino rats. The rats were randomly assigned into 5 groups, 8 each: I-Normal Control (NC) group, II-ISO-induced MI control (ISO-MI) injected with ISO subcutaneously at a dose of 100 mg/kg to induce experimental AMI, III-A- Metformin treated ISO-induced MI group (300 mg/kg/day), III-B-Sitagliptin treated ISO-induced MI group (10 mg/kg/day) and III-C- Dapagliflozin treated ISO-induced MI group (5 mg/kg/day).

Results: Treated groups showed significant improvement at \( p < 0.05 \) of ECG parameters with a decrease HR, ST amplitude and QT interval as compared to ISO-MI group. There was significant reduction at \( p < 0.05 \) of serum levels of IL-1β, troponin I and caspase 3 in the treated groups.

Conclusions: All medications proved to be effective in alleviating the harmful effects caused by ISO-induced MI evidenced by ECG readings and biochemical parameters. However, Dapagliflozin demonstrated a superior effect to Metformin and Sitagliptin.

Keywords: Acute myocardial infarction, Antidiabetic cardioprotective effect, ECG

Background

Coronary heart disease (CHD) is one of the leading causes of disability and death. Every one in five deaths that occurs worldwide are attributed to an acute myocardial infarction (AMI) (Taghipour et al. 2018; El-Moselhy et al. 2018). Although mortality from AMI has been reduced in recent years, morbidity remains high; in the form of cardiogenic shock, ventricular septal rupture, acute mitral regurgitation, and right ventricular infarction (Bajaj et al. 2015).

AMI is the irreversible necrosis of the cardiomyocytes resulting from extended myocardial ischemia (Frangogiannis 2015). A pro-inflammatory response is initially induced by the onset of myocardial ischemia. Inflammation aims at removing necrotic cell debris from the AMI zone. Regulated processes: including complement cascade activation, reactive oxygen species (ROS) production, and release of damage associated molecular patterns (DAMPs), control this phase through the production of...
different pro-inflammatory mediators, such as Interleukin-1 (IL-1); regarded as the main cytokine mediating pro-inflammatory response, IL-6 and IL-8 as well as tumor necrosis factor-α (TNF-α) (Ong et al. 2018), cells; mainly cardiomyocytes (Frangogiannis 2015), resident macrophages of the tissues (Chiou et al. 1995), endothelial cells (Prabhu and Frangogiannis 2016), and neutrophils (Prabhu and Frangogiannis 2016). Consequently, the ischemic injury will expand past the original MI zone as the infiltrating leukocytes incite cardiomyocytes death by attacking the viable border around the original diseased area (Ong et al. 2018).

A reparative anti-inflammatory phase usually follows, which allows healing of the wound and scar formation (Ong et al. 2018). Apoptosis of neutrophils is considered the central mechanism of resolution of inflammation (Ortega-Gómez et al. 2013). There are a multitude of pathways that activate apoptosis, most essentially leading to the activation of caspases (Obeng 2021). In general, caspase-mediated apoptosis pathways usually converge on a common effector caspase, such as casp-3, to execute the apoptotic function (Kim and Kang 2010). This process was found to be present in the early phase in the border zone of the infarcted myocardium, emphasizing its crucial role in acute myocardial loss after AMI (Olivetti et al. Bulletin of the National Research Centre (2022) 46:123).

Anti-diabetic drugs affect the cardiovascular risk of diabetic patients, lately this impact was shown to be mostly independent of their glucose-lowering effects (Younk et al. 2016). Metformin, commonly prescribed for type 2 diabetes, acts as an insulin sensitizer by stimulating muscle and hepatic AMP-activated protein kinase (AMPK). Metformin possibly suppresses inflammatory response by inhibition of NFκB through AMPK-dependent and independent pathways. It was shown to inhibit inflammatory response via AMPK-phosphatase and the tensin homolog pathway in rat smooth muscle cells (Kim and Choi 2012). Furthermore, metformin reduces the production of NO, prostaglandin E2 and pro-inflammatory cytokines such as IL-1β, IL-6 and TNF-α through inhibition of NFκB activation in macrophages (Saisho et al. 2003).

Dapagliflozin belongs to another antidiabetic drug class; the sodium glucose transporter 2 (SGLT2) inhibitors. It blocks the renal SGLT2 co-transporter that is responsible for reabsorption of 90% of the glucose, therefore it will selectively inhibit the reuptake of sodium and glucose within the early proximal convoluted tubule of the kidney, and this will lead to further reduction of the renal threshold for glucose and hence, an increase in the excretion of glucose in the urine (Fioretto et al. 2015). SGLT-2 does not exist in cardiac tissues; therefore the anti-inflammatory potential of dapagliflozin occurs independent to SGLT-2 (Lahnwong et al. 2018a). The anti-inflammatory effect of dapagliflozin is mediated mainly through increasing the M2/M1 phenotype macrophage ratio; subsequently dapagliflozin increases the anti-inflammatory cytokine mRNA levels such as IL-10 and decreased inflammatory cytokines mRNA levels such as IL-1β and IL-6 (Gordon 2003).

Based on the current knowledge, this study aimed to assess the effect of metformin, sitagliptin and dapagliflozin on electrocardiogram (ECG) changes, IL-1β, cardiac troponin I (cTn-I), caspase 3 in isoprenaline (ISO) induced MI in rats.

**Methods**

**Drugs**

ISO was purchased from Sigma-Aldrich, USA; Metformin (Glucophage®) from Bristol-Myers Squibb; Sitagliptin (Januvia®) from Merck Sharp and Dohme; and Dapagliflozin (Farxiga®) from Astrazeneca pharmaceuticals LP.

**Animals**

The present study was conducted on 40 adult male Wistar albino rats, 6 to 7 months old, weighing between 200 and 250 g each. The rats were kept under standard laboratory conditions of light, temperature, and humidity with free access to food and water in well ventilated animal cages, each cage housed five animals. The rats were purchased from the animal house of the Medical Physiology Department, Alexandria Faculty of Medicine. All experimental procedures were approved and performed in compliance with the guidelines of the Local Ethics Committee of Alexandria Faculty of Medicine, University of Alexandria (IRB code 00012098-FWA: No. 00018699; membership in International Council of Laboratory Animal science organization ICLAS). All experimental procedures were strictly carried out following the ethical guidelines.
Study design
After 7 days of acclimatization, rats were randomly assigned into 5 groups, 8 each: I-Normal Control (NC) group, received 2 ml of 2% gum acacia (GA) orally for 14 days then injected with 1 ml saline SC in the last two days; II-ISO-induced MI control (ISO-MI), received 2 ml of 2% gum acacia orally for 14 days then injected with ISO subcutaneously at a dose of 100 mg/kg body weight dissolved in 1-ml normal saline to induce experimental AMI, in the last 2 day (El-Gohary and Allam 2017). In the ISO-induced MI treated groups; all rats were injected with ISO as previously described in the last 2 days: III-A- Metformin treated group, received metformin suspended in 2% gum acacia orally in a dose of 300 mg/kg/day for 14 days (Whittington et al. 2013), III-B- Sitagliptin treated group, received sitagliptin suspended in 2% gum acacia orally in a dose of 10 mg/kg/day for 14 days (Ibrahim et al. 2018); III-C-Dapagliflozin treated group: received dapagliflozin suspended in 2% gum acacia orally in a dose of 5 mg/kg/day for 14 days (Durak et al. 2018).

For assurance of experimental AMI induction by ISO, some rats were dissected 24 h after the last ISO dose to assess AMI macroscopically (Fig. 1).

ECG recording and analysis
Twenty-four hours after the last ISO injection, ECG was performed on all the rats using the Powerlab system (Transonic System Inc., USA). Ketamine (80 mg/kg) and xylazine (10 mg/kg) were injected intramuscularly for induction of anesthesia, analgesia, and muscle relaxation (Veilleux-Lemieux et al. 2012). The ECG electrodes were inserted subcutaneously in the anaesthetized rat’s limbs in supine position for recording. ECG was recorded continuously for 3 min in each rat with standard artifact free lead II (right forelimb to left hind limb) as lead II is sufficient for the general analysis of ECG parameters in rodents (Konopelski and Ufnal 2016). Heart rate (HR), R-R, QT intervals, R wave amplitude and ST segment were calculated from ECG recordings (Moradi-Arzeloo et al. 2016).

Laboratory estimates
After ECG recording, whole blood specimens were collected from retro-orbital venous plexus via capillary tube. Sera were separated by centrifugation at 1000×g for 15 min. Separated sera were stored at −80 °C until further biochemical analysis (El-Gohary and Allam 2017). Rats were sacrificed afterwards by decapitation. C_Tn-I (Abcam, Cat. No. ab246529), IL-1β (Sigma-Aldrich, Cat. No. RAB0311) and Caspase-3 (My Biosource, Cat. No.MBS261814) were measured in serum by the corresponding ELISA kits according to the manufacturer’s manual. Results were expressed in pg/ml.

Statistical analysis of the data
Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp). The Kolmogorov–Smirnov test was used to verify the normality of distribution Quantitative data were described using range (minimum and maximum), mean, standard deviation, median and interquartile range (IQR). All tests were two-tailed and P values < 0.05 were considered statistically significant. F-test (ANOVA) was used for normally distributed quantitative variables, to compare between more than two groups, and Post Hoc test (Tukey) for pairwise comparisons.

Results
Changes in ECG tracing
Baseline ECG parameters were R-R interval (0.27±0.02) and QT interval (0.043±0.008). After ISO injection there was significant decrease of R-R interval to a mean value of (0.22±0.01) and increase of QT interval (0.095±0.005) (P<0.001). However, fourteen days of oral treatment with metformin, sitagliptin or dapagliflozin were associated with a significant increase in R-R interval by 9%, 13% and 27%, respectively, and a reduction in QT interval by 22%, 33% and 47%, respectively, as compared to ISO-induced MI group (Table 1; Figs. 2A and 3).

The mean values in normal control group were (247.4±31.68), (528.8±51.39) and (94.74±29.19) for HR, R amplitude and ST amplitude, respectively.After MI induction by ISO injection there was significant increase of HR (287.7±16.72) (P<0.001), reduction in mean value of R wave amplitude (308.4±7.86) (P<0.001) and significant increase in ST segment (131.0±13.09) as compared to normal control rats. However, fourteen days of oral treatment with metformin, sitagliptin or dapagliflozin
Table 1 Comparison between the different studied groups according to different ECG parameters

|                  | Normal control | ISO induced MI | Metformin | Sitagliptin | Dapagliflozin | F     | p    |
|------------------|----------------|----------------|-----------|-------------|---------------|-------|------|
| R-R (s)          | 0.27±0.02      | 0.22±0.01      | 0.24±0.01 | 0.25±0.02   | 0.28±0.01     | 19.029| ≤0.05|
| HR (bpm)         | 247.4±31.68    | 287.7±16.72    | 256.0±13.98 | 236.5±23.22 | 223.4±10.15  | 13.858| ≤0.05|
| QT (s)           | 0.043±0.008    | 0.095±0.005    | 0.074±0.006 | 0.063±0.007 | 0.050±0.007  | 96.537| ≤0.05|
| R (mv)           | 528.8±51.39    | 308.4±7.86     | 376.1±22.86 | 465.6±76.63 | 490.0±54.8   | 33.304| ≤0.05|
| ST (mv)          | 94.74±29.19    | 131.0±13.09    | 100.6±9.03 | 94.53±16.12 | 44.23±27.09  | 23.168| ≤0.05|

F: F for ANOVA test, Pairwise comparison bet. Each 2 groups was done using Post Hoc Test, (Tukey)

*Statistically significant at p ≤ 0.05, *: Significant between C-ve and each other group

$: Significant between C+ve and each other group, $: Significant between Metformin and each other group

$: Significant between Sitagliptin and Dapagliflozin

Fig. 2 ECG tracing in the different studied groups: a Normal control group, b ISO induced MI, showing significant increase of HR, decrease of R amplitude and elevation of ST segment as compared to normal group, c Metformin treated group, d Sitagliptin treated group, e Dapagliflozin treated group showing significant reduction of HR, ST amplitude and QT interval as compared to other treated groups
were associated with a significant reduction in HR by 11%, 17% and 22% respectively. However, R amplitude was significantly increased by 22%, 51% and 59%, and ST amplitude was significantly decreased by 23%, 28% and 66%, respectively, as compared to ISO-induced MI group (Table 1; Figs. 2B and 3).

Biochemical laboratory estimates

Changes in IL-1β level

ISO-induced MI control group showed a statistically significant increase in the level of IL-1β (134.0 ± 5.16) when compared to the normal control group (111.6 ± 6.24) (P < 0.001). However, treatment leads to significant reduction of serum IL-1β to a mean value (126.7 ± 4.22), (121.5 ± 4.74) and (116.8 ± 4.69) with metformin, sitagliptin and dapagliflozin, respectively. When comparing the treated groups to the normal control group; IL-1β level was still significantly higher in metformin and sitagliptin treated groups (P < 0.001), on the other hand dapagliflozin treated group showed no statistically significant difference (Fig. 4).

Changes in casp-3 level

Apoptosis was biochemically evident by a nineteen folds increase in Casp-3 level from a mean value of (842.3 ± 28.28) in normal control group to a mean value

![Graph A](image1.png)

![Graph B](image2.png)
of (1002.3 ± 5.56) in ISO-induced MI control group. However, treatment of the MI rats with metformin, sitagliptin and dapagliflozin lead to downregulation of Casp-3 with mean values of (945.4 ± 19.60), (916.3 ± 26.20) and (879.1 ± 26.10), respectively. Dapagliflozin-treated group showed a significant decrease in the casp-3 level as compared to metformin and sitagliptin treated groups (P < 0.001) (Fig. 4).

**Changes in cTn-I level**

The assessment of cTn-I level as a marker of myocardial injury was done. ISO-induced MI control group showed a statistically significant increase in the level of cTn-I (820.5 ± 13.84) when compared to the normal Control group (724.3 ± 8.60) (P < 0.001). Additionally, treatment with metformin, sitagliptin and dapagliflozin were associated with significant reduction of cTn-I to mean values of (783.6 ± 13.25), (767.0 ± 20.01) and (750.1 ± 14.26) respectively when compared to ISO-induced MI control group (P < 0.001). Dapagliflozin-treated group showed a significant decrease in the cTn-I level when compared to metformin treated group (P < 0.001) (Fig. 4).

**Discussion**

The initial pathological event in myocardial infarction (MI) is ischemia (Steffens et al. 2009). It induces a protective pro-inflammatory response. However, the excessive production of inflammatory mediators such as IL-1β and IL-6 will often lead to an increase in the size of MI by inducing the death of cardiomyocytes (Ong et al. 2018). Therefore, targeting this inflammatory process is considered an important therapeutic strategy to limit the size of the MI (Ong et al. 2018). Different anti-diabetic drugs, such as biguanides (Metformin), DPP-4 inhibitors (Sitagliptin) and SGLT2 inhibitors (Dapagliflozin) have an anti-inflammatory potential, which possibly gives these drugs a positive effect on cardiovascular parameters independent of their glucose lowering effect (Kothari et al. 2016). We investigated the effect of Metformin, Sitagliptin and Dapagliflozin on experimentally induced MI in non-diabetic rats, expressed by effect on ECG changes, IL-1β, cTn-I and casp-3.

In the present study, ISO administration resulted in significant alterations in ECG patterns when compared to the normal control group. The changes included ST segment elevation which reflects the potential difference in the boundary between ischemic and non-ischemic zones, decreased R wave amplitude due to myocardial edema. Increase HR was evident resulting from positive chronotropic effect of ISO that lead to inadequate blood flow to the heart and coronary hypoperfusion. In addition, ISO administration caused QT interval prolongation related to ventricular functional abnormality due to oxidative stress and as a consequence membrane damage could be a potential risk for ventricular arrhythmia and sudden cardiac collapse and finally shortened R-R interval due to increased HR. These changes were attributed
to the potential ischemia and infarction induced by ISO (Moradi-Arzeloo et al. 2016).

ISO-induced MI control group showed a statistically significant increase in the level of cTn-I, IL-1β and casp-3 when compared to the normal control group. The significant increase in serum levels of cTn-I was expected as cardiomyocyte damage due to excessive production of ROS and cytotoxic free radicals in ISO induced MI resulted in the disruption of the integrity and function of myocardial membranes, releasing intracellular cardiac enzymes such as the cTn-I (Huang et al. 2018). IL-1 significant elevation is supported by Huang et al. (2018), as ISO administration resulted in increased production of pro-inflammatory cytokines such as IL-1β explained by phosphorylation of NF-κB and its translocation from the cytoplasm to the nucleus induces overexpression of pro-inflammatory cytokines (Ojha et al. 2015). IL-1 is an essential player in the stimulation of the inflammatory response post-infarction and cardiac remodeling (Ong et al. 2018). Casp-3 is perceived to be the most important casp of the terminal apoptotic pathway (Kim and Kang 2010). Its serum level increase during an MI due to mitochondrial and lysosomal destabilization (Sahu et al. 2014).

After Metformin treatment, significant improvement in cardiac ECG parameters such as lower ST segment elevation, higher R wave amplitude, slower HR, prolonged R-R and shortened QT interval were detected in comparison to ISO group; thus, reducing the myocardial oxygen consumption and the extent of necrosis. Similar normalization of the prolonged QT interval and shortened R-R interval were noticed in doxorubicin induced abnormal ECG (Emeka and Al-Ahmed 2017). These cardioprotective effects were explained by the anti-inflammatory, anti-apoptotic and antioxidant properties of metformin (Soraya et al. 2012; Al-Kuraishy and Hussein 2017). Zhang et al. (2020) elaborated that Metformin can activate AMPK and inhibit NLRP3 inflammasome activation in myocardial infarction manifested by decreased level of IL-1, in accordance with our results. Likely, Al-Kuraishy and Hussein (2017) showed that pretreatment with Metformin could offer significant cardioprotection by reducing the levels of casp-3 and cTn-I in doxorubicin induced cardiotoxicity in rats due to AMPK activation. While Al Rasheed et al. (2018) described lower cTn-I and CK-MB in ISO induced MI by the ability of metformin to inhibit NF-κB activation in vascular smooth muscle cells and endothelial cells. Moreover, the opening of the mitochondrial Permeability Transition Pore protein (mPTP); responsible for reperfusion injury, is regulated mainly by phosphoinositide 3- kinase (PI3K) and protein kinase B (Akt) pathways. It was shown that Metformin could stimulate downstream kinases of the Reperfusion Injury Salvage Kinase (RISK) pathway and increase Akt phosphorylation if administrated during reperfusion, subsequently preventing the opening of the mPTP’s (Bhamra et al. 2008).

Comparably pretreatment with Sitagliptin significantly lowered ST segment elevation, increased R wave amplitude, decreased HR, prolonged R-R and shortened QT interval when compared to ISO-treated group. Khodeer et al. (2019), El-Bakly (2015) and El-Agamy et al. (2016) exhibited similar ECG results. Pretreatment with Sitagliptin reduced cTn-I when compared to ISO induced MI group, this finding was previously explained by its ability to activate c-AMP dependent protein kinase by GLP-1 (El-Bakly 2015), and phosphatidylinositol 3-kinase (PI 3-kinase) which are responsible for protection against ischemia reperfusion (I/R) injury (Bose et al. 2005). IL-1β serum level was also significantly less than in the untreated ISO group in our study, and along with other inflammatory cytokines such as IL-6 and TNF-α as it was found to suppress NF-κB activation and its translocation to the nucleus in the cardiomyocytes (Lin and Lin 2016). Chang et al. (2013) communicated that Sitagliptin could reduce myocardial injury and apoptosis in I/R injury rat model by increasing phosphorylation levels of Akt and Bax associated with reducing expression levels of Casp-3, as proven in our study. Moreover, Sitagliptin could up-regulate Bcl-2 expression, resulting in decreased Bax/Bcl-2 ratio in I/R rats through activation of PI3K/Akt pathway.

Dapagliflozin treated group showed significant improvements in all recorded ECG parameters when compared to the ISO group. Consistent with our findings, Durak et al. (2018) reported that treatment with Dapagliflozin improved the prolonged QT-interval in ECG as it attenuated the augmentation of depressed voltage-gated K⁺-channel currents which resulted into improving the prolonged ventricular repolarization. Moreover, Dapagliflozin treated group was found to have significantly larger R wave amplitude when compared to Metformin treated group; possibly due to the capacity of Dapagliflozin to decrease cardiac mitochondrial dysfunction, reduce mitochondrial ROS production and attenuate cardiomyocyte apoptosis (Aarsman and Bosch 1981). Also, Dapagliflozin had a significantly lower HR; and consequently, longer R-R interval; when compared to Metformin treated group. The ability of Dapagliflozin to delay time of onset of first ventricular tachycardia and ventricular fibrillation which occurs usually as a complication of MI and lower arrhythmia score is a rational explanation to this finding (Aarsman and Bosch 1981).

Finally, Dapagliflozin treated group showed a significant decrease in the QT interval as compared to the
Metformin and Sitagliptin treated groups. Dapagliflozin augmentation of certain ionic channels explains its better results as treatment with Dapagliflozin was associated with improvements in prolonged ventricular repolarization due to the augmentation in depressed voltage-gated K⁺-channel currents (Health and Population 1984).

While Agoestina and Keep (1984) showed that Dapagliflozin could effectively lower the CTn-T, in accordance with our results by stabilizing the myocardial membranes; Lee et al. (2017) demonstrated reduced IL-1β as assured by our findings, increased IL-10, as well as increased ratio of M2/M1 phenotype macrophage by reason of Dapagliflozin ability to stimulate polarization of macrophages to an anti-inflammatory phenotype (Lahnwong et al. 2018b). Tanjak et al. (2018) demonstrated that 4 weeks treatment with Dapagliflozin in rats with myocardial I/R injury could decrease the levels of casp-3 as we demonstrated and decrease Bax/Bcl-2 ratio since Dapagliflozin suppresses the endoplasmic reticulum stress pathway stimulated by hypoxia and ROS exposure which results in abnormal protein folding and maturation leading to apoptosis (Shih et al. 2020).

Conclusions
This study explored the cardioprotective effects of different classes of oral antidiabetic drugs in non-diabetic rats. All medications proved to be effective in alleviating the harmful effects caused by ISO evidenced by ECG readings and biochemical parameters. However, Dapagliflozin seems to be superior to Metformin and Sitagliptin.

Abbreviations
AMI: Acute myocardial infarction; AMPK: AMP-activated protein kinase; CHD: Coronary heart disease; CTn-I: Cardiac troponin I; DAMPs: Damage associated molecular patterns; ECG: On electrocardiogram; GA: Gum acacia; GLP-1: Glucagon-like peptide-1; HR: Heart rate; I/R: Ischemia reperfusion; ISO: Isoprenaline; ISO-MI: ISO-induced MI control; MI: Myocardial infarction; NC: Normal control; ROS: Reactive oxygen species; SGLT2: Sodium glucose transporter 2; Th1: Type 1 helper T cell; TNF-α: As tumor necrosis factor-α.

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Author contributions
MI, MK and MM had substantial contributions to the conception and design of the work. All authors were responsible for the acquisition, analysis, and interpretation of data for the work. SE and NB were responsible for drafting the corresponding author on reasonable request.

Declarations

Ethical approval and consent to participate
This an experimental animal study. All experimental procedures were approved and performed in compliance with the guidelines of the Local Ethics’ Committee of Alexandria Faculty of Medicine, University of Alexandria (IRB code 00012098-FWA: No. 00018699; membership in International Council of Laboratory Animal science organization (ICLAS). All experimental procedures were strictly carried out following the ethical guidelines.

Consent for publication
Not applicable.

Competing interests
The authors declare they have no competing interests.

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