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Research article

Investigating the effect of some fluoroquinolones on C-reactive protein levels and ACh-Induced blood pressure reduction deviations after aging of diabetes in STZ-Induced diabetic wistar rats

Hussam M. Gharib [a,*], Mohammad Y. Abajy [b], Abdulnaser Omaren [a]

[a] Department of Pharmacology, Faculty of Pharmacy, Damascus University, Syria
[b] Department of Biochemistry, Faculty of Pharmacy, Aleppo University, Syria

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ABSTRACT

The treatment of infections in diabetic patients by fluoroquinolone antibiotics is associated with a reduced risk of coronary artery disease, and may improve endothelium-derived hyperpolarizing factor (EDHF) efficacy. The inflammatory marker C-reactive protein (CRP) is an important predictor of cardiovascular events, and vascular endothelium dysfunction, which makes this marker a target for drug-based treatment. This study aims to investigate the relation between the treatment by fluoroquinolones with CRP plasma levels, as well as acetylecholine (ACh)-induced small conductance calcium-activated potassium channels (SK_{Ca})-dependent blood pressure (BP) reduction deviations in wistar rats after inducing a type 2-like diabetes with aging state after four months of streptozotocin (STZ) injection. Experimental animals were divided into four groups, group 1: diabetic animals were treated with moxifloxacin (n = 15), group 2: diabetic animals were treated with levofloxacin (n = 15), group 3: diabetic control animals (n = 15), and group 4: non-diabetic control animals (n = 6). The levels of plasma CRP, as well as ACh-induced SK_{Ca}-dependent BP reduction deviations were compared four months after the development of diabetes, after that; two groups were treated with fluoroquinolones, four months after the treatment; CRP-plasma levels, as well as ACh-induced SK_{Ca}-dependent BP reduction deviations were also evaluated and compared for all groups. Sustained hyperglycemia after the induction of diabetes elevated CRP plasma levels, and reduced ACh-induced SK_{Ca}-dependent BP reduction, observed diabetes-induced variations were minimal in fluoroquinolones treated diabetic groups compared with diabetic control group, In conclusion, the treatment with fluoroquinolone antibiotics in diabetic wistars may be associated with a lowering in CRP levels progression, and improvement in SK_{Ca} vitality, which indicates the importance of treating infections in diabetics by fluoroquinolones to mitigate some vascular complications signs that lead to morbidity and mortality in diabetes.

1. Introduction

Diabetes is a growing disease in terms of the number of patients and the percentage of the population. The total number of diabetics worldwide has quadrupled in the last three decades, therefore, there is a continuous increase in morbidity and mortality in diabetics due to the combination of several genetic, environmental, and lifestyle factors [1]. The growth rate in diabetic population in developing countries is the highest in the world [2, 3]. Diabetes is associated with atherosclerotic vascular lesions which cause macro- and micro-vascular complications, which in turn end with the most rate of diabetic morbidity and mortality [4]. Deaths due to cardiovascular causes in diabetic patients are estimated to be about 80% of all diabetic mortality [5], most of which are of coronary artery origin [6]. In a previous study in Netherlands (2002), there was a decreased incidence of coronary artery disease in patients with type 2 diabetes, who had been treated with fluoroquinolone antibiotics within the past three years, using the fluoroquinolone doses usually prescribed in medical practice as antibiotics. This result was not obtained in the groups of diabetics, who had been treated with several other categories of antibiotics [7]. As shown in another study in Aleppo university-Syria (2012) on experimental animals, an improved vascular function of EDHF was associated with the treatment of STZ-induced diabetic wistar rats with fluoroquinolone antibiotics, which was due to the enhancing of the pivotal function of SKCa channels [8]. However, these studies did not determine the effect of fluoroquinolones on plasma

* Corresponding author.
E-mail address: dr.hosam1977@gmail.com (H.M. Gharib).

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concentrations of CRP in these patients. Like other coronary artery disease markers, CRP is an inflammatory marker and an important predictor of both cardiovascular and coronary artery diseases [9, 10], which directly related to endothelial function, and SKCa viability, especially in diabetes [11]. CRP plasma concentration reduction plays an independent role in increasing cardiovascular benefits from the reduction of other risk factors [12], which makes CRP plasma levels reduction considered as a pharmacotherapy essential target [13]. To investigate the effect of fluoroquinolones on CRP plasma levels, and SKCa viability, STZ-induced diabetic wistar rats were treated with one of two common fluoroqinolone antibiotics: (moxifloxacin, or levofloxacin), CRP plasma levels, as well as SKCa-induced BP reduction deviations, were evaluated and compared with the studied groups before, and after the treatment with fluoroquinolones.

2. Materials

STZ: Sigma-Aldrich, UK.

Levofloxacin, Moxifloxacin: Ibn-Elhaytham pharmaceutical industries company, SAR.

3. Methods

3.1. Animals and induction of diabetes

Experimental protocols were approved by the faculty of pharmacy, Aleppo university, Syria. 51 male albino wistar rats (88–115 gr), were housed under the following conditions: 25 ± 2 °C, humidity of 55 ± 5%, and a 12/12-hour light/dark cycle, a three-month high-fructose feeding, casein, and fat (20%) diet. Rats were intraperitoneally injected with 60 mg/kg STZ divided into two equally doses with a 12-h interval [14], and supportive low doses (20–30 mg/kg) two weeks after the first STZ injection for some animals was needed [15, 16]. STZ was dissolved in citrate buffer according to Sigma-Aldrich parameters at pH = 4.5 [17], Serum level of fasting blood glucose (FBG) was adopted at the level over than 200 mg/dl [17]. we waited for four months after induction of diabetes, to promot the diabetic complications [18, 19]. All the animals were allowed free access to bottles of water, and diet-containing plates, and maintained in aerated plastic cages, as per the guidelines of Institute Animal Ethics Committee of Aleppo university, (Resolution No: 862/I). rats were randomly divided into four groups:

- Group 1 (n = 15): rats were intraperitoneally injected with moxifloxacin, one daily dose of 80 mg/kg, which was equivalent to human levels for 800 mg/d, depending on the similarity in the main pharmacokinetic parameters [20].
- Group 2 (n = 15): rats were intraperitoneally injected with levofloxacin, one daily dose of 100 mg/kg, which was equivalent to human levels for 1000 mg/d, depending on the similarity in the main pharmacokinetic parameters [20].
  - ✓ The injection of fluoroquinolones lasts for 14 days, which is a sufficient time to treat bacterial infections using these compounds [21, 22]; fluoroquinolones were dissolved in phosphate sodium buffer at pH = 7.3, which is a protocol according to Sigma-Aldrich parameters in dissolving fluoroquinolone derivatives [23].
- Group 3 (n = 15): rats were injected with the same volume of phosphate buffer, and were considered as diabetic controls.
- Group 4 (n = 6): non STZ treated normal rats were injected with the same volume of phosphate buffer, and were considered as non-diabetic controls.

4. Measurements

4.1. Blood glucose measurements

Blood glucose levels were measured using a portable One Touch Sure Step Glucose meter (Accu-Chek® Active, Roche, Germany), which was commonly used in clinical practice; blood glucose levels were measured after fasting for 12 h, to avoid the effects of anesthesia on the blood glucose levels, no anesthesia was used at the time of the measurement.

4.2. PH measurement

The pH of solutions was adjusted using GLP 21 pH-meter (CRISON, Spain).

4.3. Weights measurement

Weights of animals, and pharmaceutical materials were measured using AS/220/C/2 RADWAG, Poland.

4.4. Blood sampling

Blood samples of the experimental wistar rats were collected by retro-orbital sinus puncture, via the medial canthus of the eyes, using sterilized heparinized microhematocrit tubes, where 1 ml of blood was obtained for analysis after a 12-h overnight fast, and the blood was then centrifuged at 3,000 rpm for a period of 10 min to obtain the serum, using Stuart Microfuge-SCF2, BioCote, UK.

4.5. Insulin measurement

Insulin levels were measured in serum samples by a sandwich enzyme immunoassay procedure, using Ultra Sensitive Mouse Insulin ELISA Kit (Crystal Chem, Inc, Illinois, USA), with a microplate reader (Multiskan EX Microplate Photometer, Thermo Scientific, Schwerte, Germany).

4.6. CRP measurement

For the measurement of CRP, particles coated with anti-CRP antibodies were used, which were agglutinated by CRP molecules present in the serum samples. Since the agglutination causes changes in the absorbance proportionally to the concentration of CRP, and after comparison with a calibrator, it was possible to determine the exact concentration of CRP in each serum sample. This test was carried out with the kit CRP-TURBI, SPINREACT, Spain, and using the reader BTS-350, BioSystems [24].

4.7. BP measurements by CODA technique

Tail-cuff measurements was carried out using CODA 8 BP recording technique (Kent Scientific, Torrington, CT, USA), this system uses volume pressure recorder (VPR) to detect BP based on changes of volume in the wistars tail, CODA system was used as follows; patency of the occlusion cuffs (OC), and VPR cuffs was tested before each experiment, all experiments were performed in a quiet place at (22 ± 2 °C), rats were allways acclimatized for half an hour period before the experiments, after that, experimental protocols were conducted as follows, rats were inserted into a canister-like tubes, all holders of tubes were checked to prevent wistars movements, the OC was placed at the base of the wistar tail, the VPR cuff-sensor was placed next to the OC, base plates were preheated to 35 °C, studied wistars were warmed for 10 min before, and throughout BP recordings, the OC was inflated to maximum value (250 mmHg), and then deflated over 20 s, the sensor of VPR cuff detected changes in the blood volume through the tail during the OC deflation, each session consisted of 20 cycles per set, rats were habituated for mentioned tubes, and for BP measurements [25].

4.8. SK_{Ca} channels blockage

- Pressure values of experimental animal groups were measured by CODA technique as mentioned above.

Table 1. Shows the differences in parameters after the induction of diabetes.

Studied group	Group-1 (n = 15)	Group-2 (n = 15)	Diabetic Controls (n = 15)	Normal Rats (n = 6)	p-value/F
Weights ±SD (gr)	165.07* ±11.94	162.27* ±16.49	166.13* ±16.32	239.83 ± 20.98	$p < 0.01/F = 40.30$
FBG ±SD (mg/dl)	247.60* ±24.87	248.13* ±23.11	238.00* ±27.22	77.83 ± 10.30	$p < 0.01/F = 85.87$
Insulin levels ±SD (μU/mL)	6.60* ±1.21	6.18* ±1.12	6.43* ±1.47	17.01 ± 2.34	$p < 0.01/F = 97.69$
CRP levels after diabetes development ±SD (mg/L)	0.47 ± 0.31	0.42 ± 0.34	0.38 ± 0.25	0.23 ± 0.12	$p > 0.05/F = 0.389$
CRP levels after fluoroquinolones treatment ±SD (mg/L)	1.45* ±0.49	1.47* ±0.47	1.55* ±0.51	0.52 ± 0.41	$p < 0.01$ (for diabetic groups) $p > 0.05$ (for normal group)
CRP levels differences ±SD (mg/L)	0.98 ± 0.47	1.05 ± 0.58	1.17 ± 0.59	0.28* ±0.35	$p < 0.05/F = 4.104$

One Way ANOVA test indicated that there were a significant statistical differences in weights, FBG, insulin levels among the four studied groups, Tukey test illustrated that the significant statistical differences among the four groups were between normal rats and the three diabetic groups ($p < 0.01$), with no statistically significant differences between the three diabetic groups, for CRP plasma levels analysis, Paired Samples T-Test indicated that there were statistically significant differences for the three diabetic groups after the treatment with fluoroquinolones ($p < 0.01$), while there were no statistically significant difference for normal group.

- Pressure values were re-measured after intraperitoneal injection of ACh (10 mg/kg) [26].
- All pressure measurements were also repeated after intraperitoneal injection of apamin (0.2 mg/kg) for SKCa blockage [27, 28], and then (1 h later), intraperitoneal injection of ACh (10 mg/kg).
- BP deviations were measured depending on the equation: $(\frac{BP(ap+ACh)-BP(ACh)}{BP})$*average* (ap = apamin).
- The mentioned process was fully repeated once before fluoroquinolones treatment, and again four months after the completion of fluoroquinolones treatment as well.

4.9. Statistical analysis

Values were statistically analyzed using the (IBM® SPSS® Statistics 25) Statistical Analysis Program; the following statistical methods were performed: One-way ANOVA analysis of variance was used to illustrate the differences among the four groups in body weight changes, FBG, insulin levels, and CRP plasma levels before fluoroquinolones treatment. Tukey Multiple Comparisons Test was used to find the significant differences in mean values among the four groups. Paired Samples T-Test was used to determine the mean differences between two sets of CRP plasma levels (before fluoroquinolones treatment, and after fluoroquinolones treatment). A probability value (P) of <0.05 was considered as the minimum level of statistical significant difference. All data were expressed as means ± standard deviation (SD). The number of measurement from individual animals is given by n.

5. Results and discussion

The weights, FBG, insulin levels, and CRP levels of animals for the four studied groups were measured and presented in Table 1.

In a previous study in Netherlands (2002), coronary artery disease was decreased in patients with type 2 diabetes who had been treated with fluoroquinolone antibiotics within the past three years. This result, however, was not shown in diabetics who had been treated with several other antibiotic categories [7]. In another study on experimental animals, the treatment of STZ-induced diabetic wistar rats with fluoroquinolones may have improved the endothelial function of arterial blood vessels by promoting the action of SKCa, which constitutes a major part of EDHF function [8].

Like other coronary artery disease markers, CRP is an inflammatory marker associated with impaired endothelial function of blood vessels, as well as atherosclerosis and plaque rapture, and as a significant predictor of stable and unstable coronary artery disease [9, 10]. Dicreased plasma concentrations of CRP have a role in increasing the cardiovascular benefits of reducing other risk factors [12]. According to several studies; increased CRP plasma levels accompanied by increased morbidity and mortality in high risk patients, where it has been considered as an important and independent predictor of cardiovascular disease (CVD), stroke, diabetes progression, and metabolic syndrome, making CRP as an important predictor of the risk of CVD within the next 10 years through Reynolds Risk Score (www.reynoldsriskscore.com (2008)) [29]. Moreover, the idea of double-target treatment of statins to reduce plasma concentrations of low density lipoprotein (LDL) with reduced CRP concentrations was added to evaluate the clinical results of statin therapy [30]. Recent studies have indicated the importance of pleiotropic effect of statins, which is a beneficial effect for vascular endothelial cells independent of plasma cholesterol and LDL reduction. One manifestation of this effect is the improvement of EDHF [31]. All of the above make the reduction of CRP a target for pharmacotherapy.

To evaluate the effect of fluoroquinolone compounds on CRP, STZ-induced diabetic wistar rats were randomly divided into three groups, two of which were treated with two common fluoroquinolone compounds (levofloxacin, or moxifloxacin). CRP plasma levels were also evaluated and compared before, as well as after fluoroquinolones treatment.

In the present study, we used 60 mg/kg STZ divided into two equally doses with a 12-h interval [14], and supportive low doses (20–30 mg/kg) two weeks after the first STZ injection for some animals was needed [15], as well as a 3-month high-fat, high-fructose, and high-casein diet as an animal model of diabetes [15, 16]. This protocol aims to take advantage of the immune, and inflammatory responses of pancreatic beta cells, to match the inflammatory condition of human diabetics, and to reduce mortality, as well as to obtain stable hyperglycemia [16], an adopted diabetes model was characterized by an increase of FBG over than 200 mg/dl [17], there was a statistatically significant decrease in blood insulin levels, as well as significant reduced body weights, these two results were consistent to a previous studies [32, 33]. As previously described, which was similar to the state of patients with type 2 diabetes mellitus; diabetic state was delayed for four months in waiting for aging of diabetes due to the interaction between advanced glycation end products (AGEs) and their receptors (RAGE), thus promoting diabetic complications on various target organs, such as blood vessels and pancreas [18, 19]. CRP plasma levels were evaluated and compared, and rats were then treated with fluoroquinolones for fourteen days, by four months afterwards, CRP was re-evaluated and compared to the four groups. Our results indicated that there was a decrease in body weight in the three diabetic groups compared to the non-diabetic one after the induction of diabetes by STZ injection. The decrease in body weights in STZ-induced diabetic rats was explained by a lack of genetic expression of adiponectin receptors (ADIPORs) in fatty tissues due to a decreased bioavailability of the ADIPOR2mRNA (and less important ADIPOR1mRNA), and therefore a defect in the storage of fat, Furthermore, there were a lack of gene expression of uncoupling protein 2 (UCP2) due to decreased UCP2mRNA levels, as well as a decrease in leptin levels in fatty tissues. This protein has a common role with leptin in regulating fatty tissue mass and concentration of free fatty acids stored in it [34]. Induction of diabetes elevated CRP plasma levels, but this elevation was statically non-significant, while it was consistent with a previous study [35].

Table 2. Shows ACh-induced SKCa-dependent BP reduction deviations comparisions before fluoroquinolones treatment.

Comparisons			
Group	$(\frac{\mathbf{systolic(ap+ACh)-systolic(ACh)}}{\mathit{systolic}})_{\mathit{average}}$	$(\frac{\mathbf{diastolic(ap+ACh)-diastolic(ACh)}}{\mathit{diastolic}})_{\mathit{average}}$	$(\frac{\mathbf{mean(ap+ACh)-mean(ACh)}}{\mathit{mean}})_{\mathit{average}}$
Diabetic rats ratio (n = 43)	0.123* ±0.133	0.122 ± 0.136	0.116* ±0.080
Normal rats ratio (n = 4)	0.298* ±0.121	0.180 ± 0.140	0.231* ±0.125

Using independent t-test indicated that there was a statistically significant difference between normal and diabetic rats in mean and systolic BP deviations ($t = -2.631, p < 0.05$), with statistically non-significant differences in diastolic BP deviations ($t = -0.818, p > 0.05$).

Table 3. Shows ACh-induced SKCa-dependent BP reduction deviations comparisions after fluoroquinolones treatment.

Comparisons			
Group	$(\frac{\mathbf{systolic(ap+ACh)-systolic(ACh)}}{\mathit{systolic}})_{\mathit{average}}$	$(\frac{\mathbf{diastolic(ap+ACh)-diastolic(ACh)}}{\mathit{diastolic}})_{\mathit{average}}$	$(\frac{\mathbf{mean(ap+ACh)-mean(ACh)}}{\mathit{mean}})_{\mathit{average}}$
Moxi ratio (n = 12)	0.153 ± 0.149	0.131 ± 0.102	0.141* ±0.075
Levo ratio (n = 15)	0.065 ± 0.100	0.069 ± 0.103	0.060* ±0.061
Diabetics ratio (n = 15)	0.045 ± 0.130	0.037 ± 0.094	0.041 ± 0.068
Normals ratio (n = 6)	0.155 ± 0.221	0.163 ± 0.125	0.156* ±0.109

Using One-Way ANOVA test indicated statistically significant differences in mean BP deviations among studied groups ($F = 6.559, p < 0.05$), Tukey test indicated a statistically significant difference in mean BP deviations between moxifloxacin and levofloxacin group ($p < 0.05$), as well as between levofloxacin and non-diabetic group ($p < 0.05$), on the other hand, One-Way ANOVA test indicated statistically non-significant differences in diastolic and systolic BP deviations among the four studied groups.

Despite the importance of CRP and its close association with vascular damage, and morbidity and mortality progression [29, 30], studies contrasted in demonstrating the continuous association between the pharmacologically reduction of CRP with the protective effect of the intended category of drugs, that is: in one study it was indicated that Ramipril, which belongs to angiotensin converting enzyme inhibitors (ACEIs), did not decrease CRP plasma levels within 12-weeks treatment [13], although Ramipril is the only Angiotensin-converting enzyme inhibitor (ACEI) which has the approval from Food and Drug Administration agency (FDA) in the prevention from myocardial infarction, stroke, and death from cardiovascular causes in high risk patients [36]. However, reduced CRP was an independent target in the treatment with statins (cholesterol lowering compounds), which are used in high-risk patients to reduce morbidity and mortality independently of LDL plasma levels [31].

In this study, to evaluate the association of reduced endothelial dysfunction potential in diabetic wistars, which had been treated by fluoroquinolones, with reduced CRP plasma levels, the ratio of the increase in CRP in the four studied groups after the treatment with moxifloxacin, and levofloxacin, for sufficient time as antibiotics, according to the recommendations (14 days), was compared; CRP was re-evaluated after waiting for four months after post-treatment with fluoroquinolones; a comparison of CRP levels of non-diabetic group between the period pre- and post-fluoroqinolones treatment (i.e. a four-months interval) showed a statistically non-significant increase in CRP plasma levels, which is due to aging [37], while the increase in CRP plasma levels in the three diabetic groups within the same period was statistically significant; the increase in CRP plasma levels in the three diabetic groups was due to two factors: aging [37] and chronic hyperglycemia [35], plasma CRP levels in rats were less than 2 mg/L in all groups, which was consistent with some studies [38]. In addition, comparing the increased ratio among the four groups showed that there were a statistically significant increased ratio between diabetic groups and non-diabetic one, without a statistically significant difference among the three diabetic groups in CRP levels increasing ratio. However, this increased ratio was lower in fluoroquinolone-treated groups compared to the diabetic control group, and in turn lower in moxifloxacin group compared with levofloxacin group. These results suggest that the treatment with fluoroquinolone antibiotics in diabetic rats may be associated with a reduced increase in CRP plasma levels, although there was no statistical significance in the reduction of CRP in diabetic rats after the treatment with fluoroquinolones among the three studied diabetic groups; a similar study on more number of animals, or CRP calibration by the high sensitivity method (hsCRP), may show the differences among the studied groups more clearly.

In this study; as elucidated in some studies [39], ACh was adopted as a vasodialator, because of its clear vasculopathy-induced dysfunction in EDHF-mediated vasodialation after prolonged exposure to high blood glucose levels. There were many reports indicating that the impairement of EDHF-mediated relaxation in small mesenteric arteries of diabetic animals involved KCa channels dysfunction in endothelial cells [39, 40].

After selectively SKCa blocking by apamin [27, 28], which reduces EDHF-mediated relaxation in response to ACh [41], and some other vasodialators [42], we found that the decreased ACh-induced SKCa-dependent lowering in diastolic, systolic, and mean BP was greater in normal rats in comparison with diabetic rats, with statistically significant difference between normal and diabetic rats in mean, and systolic BP deviations (Table 2), which indicated a grater pivotal role in blocked channels (SKCa) in normal, than in diabetic rats. These results suggests that sustained hyperglycemia may impede EDHF efficacy by reducing SKCa pivotal role.

Four months after fluoroquinolones treatment; the same previous set of BP measurements were repeated. As shown in our results (Table 3), there was a decreased ACh-induced SKCa-dependent lowering in diastolic, and systolic, as well as mean BP in all groups, but this decrease was the greatest in non-diabetic wistars, which indicated a full efficacy in SKCa channels, this decrease in turn was greater in fluoroquinolone-treated diabetic wistars than in diabetic controls, and greater in moxifloxacin-treated group than in levofloxacin-treated group, with statistically significant difference in mean BP deviations between moxifloxacin and levofloxacin group, as well as between levofloxacin and non-diabetic group, on the other hand, there were no statistically significant differences in diastolic, and systolic BP deviations among the four studied groups (Table 3). These results suggests that moxifloxacin may slows ACh-induced EDHF-response

impairment in diabetic wistar rats, which may related to its beneficial effect on SKCa-mediated relaxation.

6. Conclusion

We concluded that; CRP plasma levels are increased after diabetes induction using STZ in wistar rats, CRP plasma levels are in a steady progressive increase with chronicity of diabetes, CRP plasma levels are in a steady increase with aging, regardless of other risk factors, Fluoroquinolones may alleviate CRP plasma levels elevation in diabetics; this effect is related to moxifloxacin more than levofloxacin, Aging of diabetes accompanied by SK_{Ca} dysfunction, which reduced EDHF pivotal role, fluoroquinolones treatment may induce EDHF function, which mediated by SK_{Ca} upregulation, moxifloxacin may has EDHF-promotion effect more than levofloxacin.

Declarations

Author contribution statement

H.M. Gharib: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

M.Y. Abajy: Conceived and designed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.

A. Omaren: Conceived and designed the experiments.

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Competing interest statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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