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Original Article

Cardioprotective effect Linagliptin (DPP-4 Inhibitor) against myocardial infarction induced in rats with metabolic syndrome

Pharmacology

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ABSTRACT

Background: Myocardial ischemia is one of the most serious complication that results from metabolic syndrome (MetS). MetS is usually treated by polytherapy to decrease the risk of comorbidities. Dipeptidyl peptidase -4 (DPP-4) inhibitors are commonly used to control hyperglycemia and insulin resistance associated with MetS.

Objective: The aim of the present study was to demonstrate the effect of linagliptin (DPP-4 inhibitor) on some ECG and biochemical parameters of myocardial infarction (acute myocardial ischemia) induced by isoprenaline in rats with metabolic syndrome.

Methodology: 32 male albino rats of local strain were divided into four groups, Group I (8rats): Control normal group, rats were allowed to feed normal rat chow diet and water ad libitum. Group II (8 rats): Metabolic non ischemic group, animals of this group were allowed to feed high fat diet (HFD) with sucrose in drinking water for twelve weeks. Group IIIa (8 rats): Metabolic ischemic non treated group; rats of this group were allowed to feed HFD with sucrose in drinking water for twelve weeks followed by injection of isoprenaline (85/ kg / day) S.C for two consecutive days at the last two days of study period. Group IIIb (8 rats): Metabolic ischemic group treated orally with linagliptin 0.45mg/kg once daily for 4 weeks before injection of isoprenaline.

Results: Linagliptin produced a significant reduction in heart rate and S-T segment as compared to metabolic ischemic group. In addition, it produced a significant reduction in creatine kinase myocardial band (CKMB), malondialdehyde (MDA), tumor necrosis factor α (TNFα) and significant increase in catalase enzyme level as compared to ischemic non treated group.

Conclusion: linagliptin is a promising drug for decreasing the incidence of myocardial infarction which may complicate MetS.

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Keywords: Metabolic syndrome; linagliptin; myocardial infarction.

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INTRODUCTION

Metabolic syndrome (MetS), also known as syndrome X is a cluster of metabolic abnormalities that include central obesity, hypertension, insulin resistance, and atherogenic dyslipidemia [1]. Obesity and MetS are associated with accelerated atherosclerosis and a greater incidence of coronary heart disease [2].

A higher risk of cardiovascular disease, type 2diabetes mellitus (T2DM), and an increasing prevalence of insulin resistance have all been directly correlated with visceral adipose tissue (VAT) [3]. VAT is linked to increased oxidative stress, renin-angiotensin-aldosterone system (RAAS) activation, and the synthesis of pro-inflammatory adipocytokines [4]. When energy is not utilized by the heart, epicardial fat can form a protective mechanism to store it. Nevertheless, an overabundance of energy substrate has been linked to cardiac dysfunction, and the high levels of fat accumulation in this tissue exacerbate the pro-inflammatory response, leading to increased production of tumor necrosis factor α (TNF-α), interleukin 1β, or interleukin-6 (IL-6) [5] .

Insulin resistance, which results, impairs the ability of endothelial cells to produce nitric oxide and increases the release of procoagulant substances, which in turn causes platelet aggregation. While the mitogen-activated protein kinase pathway remains unaltered in an insulin-resistant state, the Phosphatidyl inositol 3 kinase (PI3K) pathway is impacted, which results in the mitogenic effect of insulin on endothelial cells and atherosclerosis [6] . It has been demonstrated that these higher rates of atherosclerotic disease lead to a ~2-fold increase in myocardial infarction risk and a markedly raised risk of cardiovascular mortality [7].

Myocardial ischemia occurs When there is insufficient oxygenated blood flow to the myocardium to meet its immediate need for oxygen and metabolic substrates [8]. Acute myocardial infarction (AMI) happens when irreversible ischemic injury results in myocardial necrosis [9].

Rapid intramyocardial ATP depletion results from the myocardium's susceptibility to ischemia due to the absence of anaerobic metabolic pathways. However, it typically takes 40–60 minutes for ATP to completely deplete. Conversely, cellular enlargement and intracellular structural alterations begin as soon as 15 minutes following the onset of ischemia, and contractile stoppage happens after a few minutes. The buildup of H+ that results from the breakdown of ATP causes such events. Inactivation of troponin C, Na+ influx (swelling), and progressive ATP loss (inactivation of Ca^{2+} ATPases) are all brought on by low pH. The acidic environment slows down all pathways, so while all processes happen in a matter of minutes, they advance gradually [10].

Linagliptin is one of the DPP-4 inhibitors that have been approved for treating T2DM either as a monotherapy or combined with other glucose lowering agents [11]. It is well tolerated and is associated with a lower risk of hypoglycemia, more importantly it has a weight neutral effect [12].

The aim of this study is to demonstrate the effects of linagliptin on myocardial infarction induced in rats with metabolic syndrome. Myocardial infarction and the cardioprotective effect of linagliptin were assessed in the present work by ECG and biochemical measurement of serum creatine kinase myocardial band (CKMB), malondialdehyde (MDA) and catalase enzyme. In addition, the inflammatory marker, TNFα was also estimated.

MATERIALS AND METHODS

Drugs and Chemicals:

- Linagliptin (Trajenta)-Boehringer Ingelheim company, USA. - Chemical name: 8-[(3R)-3-aminopiperidin-1-yl]-7-but-2 ynyl-3-methyl-1-[(4-methylquinazolin-2-yl) methyl] purine 2, 6-dione. - Chemical formula: C25H28N8O2 - Molecular weight: 472.5 Linagliptin was supplied in the form of white to yellowish tablets, each tablet contains 5 mg linagliptin free base and was freshly dissolved in distilled water.
- Sucrose powder -Elgomhoria company, Egypt: was supplied as white crystalline powder, dissolved in distilled water and provided to animals in a concentration of 10% w/v.
- Isoprenaline (Sigma Aldrich company, USA): Isoprenaline, was supplied as white to off white powder, it was freshly dissolved in normal saline.

Experimental Design:

The present study was performed on 32 adult male albino rats of local strain with initial weight of 200-300 g. Animals were purchased from local farm in Aborawash city, Egypt. Rats were housed in polyacrylic cages, four animals per cage, and were kept under the same environmental conditions of temperature and humidity with natural light-dark cycle. Food and water were provided ad libitum throughout the experiment. The rats were divided into 4 groups, Group I (8 rats): control normal group; Normal rats were allowed to feed with normal rat chow diet and water ad libitum. Group II (8 rats): Metabolic non ischemic group; the animals of this group were allowed to feed high-fat diet (HFD) with sucrose in drinking water for twelve (12) weeks. Group IIIa (8 rats): Metabolic ischemic non treated group; rats of this group were allowed to feed HFD with sucrose in drinking water for twelve weeks followed by injection of isoprenaline (85/ kg / day) S.C for two consecutive days at the last two days of study period. Group IIIb (8 rats): Metabolic ischemic treated group; rats of this group were treated orally with linagliptin 0.45mg/kg once daily for 4 weeks after induction of metabolic syndrome then injected with isoprenaline (85/ kg / day) S.C for two consecutive days at the last 2 days of the treatment period. The dose of linagliptin was chosen as the rodent equivalent to the human therapeutic dose and were calculated according to the method given by Paget and Barnes, **[13]** who calculated the dose in relation to the animal surface area.

Induction of metabolic syndrome in experimental rats:

Rats were given a high-fat, high-sucrose diet to create a model of metabolic syndrome that mimics the course of a disease in humans naturally. Every three days, the components of the HFD (table 1) [15] were mixed to create pellets that were allowed to dry before being refrigerated until needed. Rats were allowed to feed and drink ad libitum. Sucrose was prepared daily and introduced to the animals in a concentration of 10% w/v in drinking water [14]. Both HFD and sucrose were given to the animals for 12th weeks to establish a model of metabolic syndrome [15].

Table (1): Composition of normal rat chow and high fat diet (HFD)

	Normal chow diet	High-fat diet
Kcal/g	3.78	5.17
Carbohydrates	55%	33.8%
Protein	22%	26.1%
Total fat	4%	35.5%
Fiber	6%	0.1%

Induction of myocardial infarction (acute myocardial ischemia) to metabolic syndrome induced rats:
Rats of group III (a and b) were used to establish a model of myocardial infarction to metabolic syndrome induced rats. Isoprenaline induced myocardial infarction was conducted by subcutaneous injection of isoprenaline HCL (85 mg/ kg / day) for two consecutive days with an interval of 24 hours in between for metabolic syndrome induced rats at the last two days of study period [16]. Doses of isoprenaline were calculated according to the recorded weight of each animal.

Electrocardiogram (ECG): A bipolar three-lead ECG was employed. Electrocardiogram electrodes were subcutaneously inserted into the left foreleg, right foreleg, and left thigh, respectively, to record heart rate, rhythm, and ECG waves. The equipment used was the PowerLab Data Acquisition and Analysis Systems (PowerLab 4/35 with LabChart Pro, animal Bio Amp model number FE136 by AD Instruments Australia) for recording ECG [17].

Blood sample preparation: blood samples were obtained under light anesthesia (ether) from the ophthalmic venous plexus through a retro orbital approach according to Timm, [18]. Samples were collected in test tubes for serum analysis of different biochemical parameters. Blood was allowed to clot for 30 minutes before centrifugation for 20 minutes at 3000 rpm. Then the serum was separated and immediately stored at 70Co until assayed.

Biochemical assays of myocardial infarction: All biochemical measurements of myocardial infarction were performed in the biochemistry department, faculty of medicine, Cairo university. The serum level of the myocardial injury marker CKMB was measured according to the methods described by Okinaka et al. [19] by using the commercial kit. The inflammatory marker level TNFα was measured using ELISA kits according to the manufacturer's directions [20]. Lipid peroxidation products were identified in serum by measuring malondialdehyde (MDA) levels. The thiobarbituric acid-reactive material, or MDA, was measured at 532 nm using the Niehaus and Samuelsso technique [21]. The serum level of catalase was measured according to the methods described by Sinha, [22] by using the commercial kit.

Ethical Considerations
All experimental procedures (No.2204) were carried out in compliance with the National Institutes of Health's Guide for the Care and Use of Laboratory Animals and authorized by the Research Ethics Committee of the Faculty of Medicine for Girls at Al-Azhar University.

Statistical analysis
The statistical software for social sciences, version 23.0, was used to analyze the recorded data (SPSS Inc., Chicago, Illinois, USA). The means ± standard error of means (SEM) were used to present the quantitative data. Tests were conducted as follows: When comparing more than two means, use a one-way analysis of variance (ANOVA). Post Hoc test: When comparing several variables at once, the Least Significant Difference (LSD) was employed. P-value <0.05 0.05 was considered significant. P-value >0.05 was considered insignificant.

RESULTS

I- Electrocardiogram (ECG) record (table 2):
Induction of metabolic syndrome in rats (control metabolic non ischemic) produced a significant increase in heart rate (P <0.001) and insignificant elevation in S-T segment as compared with control normal group. Induction of myocardial infarction by isoprenaline (85mg/kg) (control metabolic ischemic) did not produce a significant change in heart rate but produced significant elevation in S-T segment (P <0.001) as compared with control metabolic non ischemic group. Treatment with linagliptin produced a significant reduction in heart rate (p<0.05) and S-T segment (p<0.001) as compared with control metabolic ischemic group.

Table (2): Effect of oral treatment with linagliptin (0.45 mg/kg) on heart rate (beat/min.) and S-T segment (mv) in metabolic ischemic rats

ECG parameters	Control normal	Metabolic non ischemic	Metabolic ischemic	Linagliptin	F-test	p-value
Heart rate (beat/ min)	295.37± 22.93	376.96± 3.88 [a]	371.57± 5.50	314.14± 12.17[c]	4.793	<0.001*
S-t segment (mv)	0.03± 0.01	0.05± 0.01	0.10± 0.00 [b]	0.03± 0.01[c]	15.574	<0.001*

Data were expressed as means of 8 rats ± SEM, comparisons between different groups were carried out using one-way Analysis of Variance (ANOVA)followed by Least significant difference (LSD) multiple comparisons test. (a) Significant compared to control normal at p <0.05, (b) Significant compared to metabolic non ischemic at p <0.05, (c) Significant compared to metabolic ischemic at p<0.05.

II-Biochemical assays:

***a)* As regards CKMB, TNFα, MDA (table 3):**

- Induction of metabolic syndrome in rats (control metabolic group) produced a significant increase in CKMB, TNFα, and MDA levels as compared with control normal group ($p < 0.001$).
- Induction of myocardial infarction by isoprenaline (85mg/kg) (control metabolic ischemic group) showed a significant increase in CKMB and MDA levels (282.32 ± 13.55, 194.67 ± 7.50, respectively $p < 0.05$) whereas TNFα level showed an insignificant change as compared with metabolic non ischemic group (119.53 ± 9.21 vs 103.13 ± 9.29 respectively $p > 0.05$).
- Treatment with linagliptin produced a significant reduction in all of the above parameters level as compared with control metabolic ischemic group ($p < 0.001$).

Table (3): Effect of oral treatment with linagliptin (0.45 mg/kg) on serum CKMB (u/ml), TNFα (PG/ml) and MDA (mmol/ml) in metabolic ischemic rats

Biochemical parameters	Control normal	Metabolic non ischemic	Metabolic ischemic	Linagliptin	F-test	p-value
CKMB (u/ml)	104.38± 3.66	248.72± 10.06[a]	282.32± 13.55[b]	155.17± 7.63[c]	77.371	<0.001*
TNFα (PG/ml)	28.27± 2.07	103.13± 9.29[a]	119.53± 9.21	62.03± 5.84[c]	27.704	<0.001*
MDA (mmol/ ml)	49.55± 4.22	165.43± 8.23[a]	194.67± 7.50[b]	64.25± 5.56[c]	74.133	<0.001*

CKMB: Creatine kinase myocardial band, TNFα : Tumor necrosis factor alpha, MDA: Malondialdehyde. Data were expressed as means of 8 rats ± SEM, comparisons between different groups were carried out using one-way Analysis of Variance (ANOVA)followed by Least significant difference (LSD) multiple comparisons test. (a) Significant compared to control normal at p <0.05, (b) Significant compared to metabolic non ischemic at p <0.05, (c) Significant compared to metabolic ischemic at p<0.05.

b) As regards catalase enzyme (u/ml) (table 4):

- Induction of metabolic syndrome in rats (control metabolic group) produced a significant decrease in catalase enzyme as compared with control normal group (58.15 ± 6.69 vs120.92 ± 2.63; $p < 0.001$).
- Induction of myocardial infarction by isoprenaline (85mg/kg) (control metabolic ischemic group) produced a significant decrease in catalase enzyme as compared with metabolic non ischemic group (34.90 ± 4.07 vs 58.15 ± 6.69; $p < 0.05$).
- Treatment with linagliptin produced a significant increase in catalase enzyme as compared with control ischemic group ($p < 0.001$).

Table (4): Effect of oral treatment with linagliptin (0.45 mg/kg) on serum catalase enzyme (u/ml) in metabolic ischemic rats

Biochemical parameters	Control normal	Metabolic non ischemic	Metabolic ischemic	Linagliptin	F-test	p-value
Catalase (u/ml)	120.92± 2.63	58.15± 6.69[a]	34.90± 4.07[b]	104.38± 6.13[c]	35.326	<0.001*

Data were expressed as means of 8rats±SEM, comparisons between different groups were carried out using one-way Analysis of Variance (ANOVA) followed by Least significant difference (LSD) multiple comparisons test. (a) Significant compared to control normal at p <0.05, (b) Significant compared to metabolic non ischemic at p <0.05, (c) Significant compared to metabolic ischemic at p<0.05.

DISCUSSION

It has been established that those suffering from MetS are at higher risk of developing atherosclerotic cardiovascular diseases (CVDs) [23]. Acute myocardial infarction is one of the most frequent CVDs [24]. Myocardial infarction (MI) is known to be accompanied with several biochemical changes including; increased myocardial injury marker enzymes as creatine kinase myocardial band (CKMB) and lactate dehydrogenase (LDH), increased oxidative damage shown by increased lipid peroxidation product malondialdehyde (MDA) with reduction of the activity of the antioxidants e.g. catalase and superoxide dismutase. Moreover, increased myocardial pro-inflammatory cytokines as TNFα and IL-1b are seen [25]. The conventional test for accurately diagnosing MI in both people and animals is an elevation of the ST segment in the ECG; however, in certain instances, this marker may not be elevated [26].

Acute MI was assessed in the present work by ECG and biochemical measurement of serum CKMB, MDA and catalase enzyme. Furthermore, the inflammatory marker TNFα was also measured because, following an ischemic event, inflammation plays a critical role in causing cardiac tissue damage.

In the present study, Injection of isoprenaline to rats with metabolic syndrome caused a significant elevation of ST segment while it did not alter the increased heart rate as compared to non-ischemic MetS induced rats (control metabolic). The elevated ST segment was also reported in previous studies [27, 28]. The detrimental effect of isoprenaline on the integrity of the heart cell membrane and the resulting decrease in the ventricles' mechanical

capacity are the reasons for the elevation of the ST segment in ischemic rats[29]

As regards heart rate , previous studies showed that isoprenaline either increase [30] or decrease[31] heart rate. The differences in rats' species, in isoprenaline dosages and treatment durations, and in technique may all help to explain this disagreement.
In the present work, evaluation of oxidative stress parameters (MDA, catalase enzyme) in non-ischemic MetS induced rats revealed an elevation of serum level of MDA, with reduction of catalase enzyme activity. Moreover, the inflammatory marker; TNFα level and the cardiac injury marker; CKMB were increased as compared with control normal group. These results are in harmony with those of Rangel Silvers et al. [32], who observed that rats with MetS showed a decrease in catalase enzyme activity and catalase mRNA transcription. In addition, Naguib et al. [33] found that activity of superoxide dismutase was decreased while serum levels of MDA and nitric oxide were increased. Moreover, they added that serum LDH, cardiac troponin I, C reactive protein, TNFα and IL-6 levels were significantly higher in metabolic syndrome induced rats.
In the current study, injection of isoprenaline to MetS induced rats increased lipid peroxidation product; MDA and decreased the antioxidant catalase furtherly in comparison with metabolic non ischemic group. These effects of isoprenaline were mentioned previously by Metias et al. [30] and Gonçalves et al. [28] in their study on non-metabolic rats. As regards TNFα, isoprenaline injection in the present work showed an insignificant change in the level of that cytokine as compared with non-ischemic group. In a previous study, Feng and Li, [34] found that isoprenaline stimulated the induction of TNFα and IL-1b expressions in normal rats. As regards CKMB, injection of isoprenaline to MetS induced rats, in the present study, caused further increase in CKMB level as compared to non-ischemic MetS induced animals. This result is in agreement with Liu et al. [27] who reported an increase in several cardiac enzymes; CKMB, aspartate transaminase (AST) and LDH in isoprenaline treated animals.

The mechanism by which isoprenaline produced the previous hazardous effect on the hearts of experimental animals was explained by the following: When isoprenaline is administered, cardiac cells receive an increased amount of calcium influx and endogenous norepinephrine. Cell necrosis and the disintegration of membrane permeability barriers are the outcomes of this increase in calcium input [35]. Increased myocardial Ca^{2+} level causes excessive adenosine triphosphate (ATP) breakdown, myofilament overstimulation, an increase in contractile force and oxygen consumption, as well as cardiac muscle cell damage [36]. In addition, Isoprenaline promotes neutrophil chemotaxis by inducing the release of pro-inflammatory cytokines. When neutrophils enter an infarcted region, they can release proteolytic enzymes and produce reactive oxygen species, which can cause damage to cardiac cells [37].

In the present work, pretreatment of MetS induced rats with linagliptin for one month before induction of ischemia, demonstrated a safeguard against myocardial infarction caused by isoprenaline. When compared to the ischemic untreated group, there was a significant reduction in both heart rate and ST segment elevation. Moreover, in comparison with control normal group, linagliptin nearly restored normal ECG pattern and heart rate. As regards heart rate, Ishizue et al. [38] found that pretreatment with linagliptin produced an insignificant effect on heart rate of rats with isoprenaline induced MI.

Concerning the biochemical study, the present work showed that pretreatment of ischemic rats with linagliptin caused a significant decrease of CKMB, TNFα and MDA levels while catalase enzyme showed a significant increase as compared to ischemic untreated group. Our results are in agreement with previous studies, Ishizue et al. [38] carried out a model of isoprenaline induced MI in rats and found that linagliptin decreased the elevated serum cardiac troponin I caused by isoprenaline injection. Sravanthi et al. [39] evaluated the cardioprotective effect of linagliptin in normal and type 2 diabetic rats subjected to ischemia reperfusion injury. The authors claimed that after linagliptin treatment, the antioxidant enzymes superoxide dismutase, catalase, and reduced glutathione were shown to be elevated in both normal and diabetic animals. Additionally, linagliptin treatment reduced the levels of CKMB and LDH in diabetic rats, providing support for tissue protection.

The mechanism of suppressive effect of linagliptin on isoprenaline induced tissue injury is unclear, but at least partly explained by suppression of the hyperoxidative [38]. The cardioprotective effects of DPP4 inhibitors are maintained through 2 approaches; Glucagon like peptide-1(GLP-1) mediated mechanisms and conservation of some peptides that are physiologically degraded by the DPP4 enzyme [40]. In addition to GLP-1, other peptides such as substance P, brain natriuretic peptide, stromal cell derived factor-1α (SDF-1α), and atrial natriuretic peptide are also substrates of the DPP4 enzyme. A chemokine called SDF-1α encourages endothelial progenitor cells to migrate to the heart in order to increase angiogenesis, which in turn enhances myocardial perfusion. DPP4 enzyme substrate SDF-1α is preserved by DPP4 inhibition, which also enhances heart recovery following ischemia/reperfusion and acute myocardial infarction [41], or stroke [42].

CONCLUSION

linagliptin showed a protective effect against isoprenaline induced MI in metabolic rats. The beneficial effects of linagliptin on the heart were evidenced by a significant

reduction of ST segment elevation and heart rate as compared with ischemic non-treated group. In addition, it caused a significant decrease of CKMB, TNFα and MDA levels while catalase enzyme showed a significant increase. These results give linagliptin upper hand in treating patients with metabolic syndrome who are commonly associated with cardiovascular diseases.

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43.

الملخص العربى

التأثير الوقائى لدواء الليناجلبتين ضد احتشاء عضلة القلب المحدث في الفئران المصابة بمتلازمة ألأيض

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ملخص البحث:

الخلفية: يعتبر نقص تروية عضلة القلب من اخطر المضاعفات الناتجة عن الإصابة بداء متلازمة الايض ولذلك فأن علاج هذا الداء يستلزم أخذ مجموعه من الادويه لتقليل المضاعفات الناتجه عنه ومن هذه الادويه فأن المجموعه المثبطه لانزيم داى ببتدايل ببتايداز -4 من اكثر الادويه المستخدمه للسيطره على زيادة نسبة سكر الدم ومقاومة الانسولين المصاحبين لداء متلازمة الايض.

الهدف: تهدف هذه الدراسة الى استيضاح تأثير دواء الليناجلبتين على بعض مؤشرات احتشاء عضلة القلب المحدث بواسطة عقار الايزوبرينالين في الفئران المصابه بمتلازمة الايض عن طريق فحص رسم القلب وبعض التحاليل الكميائيه

الطرق: هذا البحث قد استخدم فيه 32 فأرا من النوع المحلى وقد قسم هذا العدد من الحيوانات على اربع محموعات . المجموعه الأولى هي المجموعه الضابطه التي لم تعطى اى دواء والمجموعه الثانيه هي مجموعة متلازمة الايض المحدث في الفئران عن طريق تغذية الحيوانات بطعام به نسبه عاليه من الدهون والسكريات اما المجموعه الثالثه فهى المجموعه المعرضه لعقار الايزوبرينالين بحقنه تحت الجلد لمدة يومين متتاليين بعد احداث داء متلازمة الايض بها والمجموعه الرابعه هي المجموعه التي تناولت دواء الليناجلبتين لمدة اربع أسابيع قبل احداث احتشاء لعضلة القلب بها بعقار الايزوبريالين.

النتائج: اظهرت نتائج هذا البحث أن دواء الليناجلبتين قد احدث انخفاضا ذا دلاله احصائيه على كلا من سرعة ضربات القلب ومقطع اس- تى عند فحص رسم القلب كما أن هذا الدواء قد احدث انخفاضا ملحوظا في التحاليل الكميائيه الخاصه باحتشاء عضلة القلب ومنها كيناز الكرياتين- عامل نخر الورم الفا – مقياس اكسدة الدهون مع زيادة ذات دلاله احصائيه في انزيم الكتالاز مقارنة مع مجموعة الحيوانات المصابه باحتشاء عضلة القلب ولم تتلق علاجا .

الأستنتاجات: دواء الليناجلبتن يعتبر من الادويه الواعده في تقليل نسبة الاصابه بمرض احتشاء عضلة القلب الناتج عن مضاعفات الاصابه بداء متلازمة الايض.

الكلمات المفتاحية: متلازمة الايض، دواء الليناجلبتين، احتشاء عضلة القلب.

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