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The Ameliorative Effect of Naltrexone/Bupropion, Liraglutide and Caloric Restriction on Blood Pressure Changes in Diabetic Male Albino Rats

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Abstract:

Introduction: Diabetes significantly increases the risk of cardiovascular diseases and death. Using medical interventions to treat diabetes to prevent or minimize negative impacts on the cardiovascular system.

Aim of the study: To assess the effects of Naltrexone/Bupropion, Liraglutide, and caloric restriction on cardiovascular outcomes in diabetic male albino rats.

Subjects and Methods: This research involves a comparison of 50 male albino rats divided into 5 groups; group I: a normal control group, group II a: a diabetic control group, group II b: a caloric-restricted group, group II c: (Naltrexone/Bupropion) treated group (1 NTX / 10 BUP, orally) and group II d: liraglutide treated group (0.3mg/kg/day, S.C). SBP, DBP, MAP, fasting glucose, serum insulin level, and measurements were taken of the lipid profile, and calculations were performed for atherogenic indices such as atherogenic index of plasma, Castelli's risk index I and II, and atherogenic coefficient.

Results: The findings showed a notable enhancement in end SBP in every intervention group in comparison to the diabetic control group (p <0.05). In terms of the ultimate MAP, there was a notable reduction in both the caloric-restricted group and the liraglutide group. The atherogenic indices showed a significant decrease when compared to the diabetic group. A strong positive relationship was found between the final MAP and AIP, with a correlation Coefficient of 0.355 (p =0.012).

Conclusions: Our study highlights the potential benefits of (NTX+BUP) and liraglutide in blood pressure reduction and improving atherogenic indices and lipid profile, suggesting further preclinical investigations to confirm the current results.

Keywords: Naltrexone/Bupropion; Liraglutide; Caloric restriction; Type 2 diabetes; Rats.

1. Introduction

Adults are more likely to experience cardiovascular events if they have hypertension, dyslipidemia, or are overweight. In addition to the risk posed by each cardiovascular risk factor, those with metabolic syndrome are 3 times more likely to develop CVD than individuals without the syndrome, according to the WHO definition of metabolic syndrome.

IR and the onset of cardiovascular disease have been linked in several ways. In particular, one of those processes occurs in the endothelium of blood vessels. Vasodilation and endothelin-mediated vasoconstriction are counteracting factors that, in a healthy state, dictate vascular tone. Blood vessels constrict rather than dilate in an IR situation because the NO signaling pathway is less activated and the endothelin pathway is more activated [1].

Obesity, impaired glucose tolerance, as well as early onset of T2DM, are all risk factors for CAD, and they all contribute to the acceleration of atherosclerosis in insulin-resistant conditions.

The activation of the hexosamine biosynthetic route is another way that excessive glucose impacts vascular parameters. This process leads to an increase in glucosamine synthesis, which in turn decreases endothelial NO generation. Advanced glycation end products (AGEs) are formed when free amino acids react with excess glucose, which happens in hyperglycemia. Interactions between AGEs and the endothelial receptor for AGE (RAGE) are associated with distinct procoagulant alterations, in accordance with the available research. In particular, the anticoagulatory protein C pathway is not activated because this interaction decreases thrombomodulin activity. Enhanced tissue factor activity is another procoagulant effect of this ligand-receptor interaction that activates coagulation factors IX as well as X via factor VIIa binding. In animal and human models, there is evidence that AGEs deactivate NO in a manner that is dependent on the dose [2].

2. Subjects and Methods

2.1 Experimental animals

The present study was conducted following the ethical guidelines set by the Fayoum University Faculty of Medical Committee. The laboratory animal house unit of Fayoum University's College of Medicine provides veterinary services. There were fifty male albino rats that weighed between 120 and 160 grams.

They are purchased from the Institute for Research on Eye Diseases in Cairo, Egypt. Each cage housed five rats.

2.2 Experimental drugs

- Streptozotocin (STZ): We purchased it from Sigma Chemical Co., located in St. Louis, Missouri, USA.
- Liraglutide: Liraglutide is available under the name of Saxenda®, and was purchased from Novo Nordisk (Denmark) in the form of a pen (6mg/ml).
- Naltrexone (NTX): naltrexone is available under the name Anarcol® and was purchased from Multi-apex Pharm, Cairo, Egypt, in the form of tablets containing 50 mg naltrexone hydrochloride.
- Bupropion (BUP): bupropion is available under the name Willenta® and was purchased from Elixir Pharma (Cairo, Egypt) as tablets containing 150 mg bupropion hydrochloride.

2.3 Experimental design

The rats were housed in separate cages, and they were maintained in comfortable temperatures in the range of 25°-30°C at the normal dark/light cycle. Rats were acclimatized for a week period during which they were given free access to regular rat chow and water and were handled regularly to minimize the effect of stress during the subsequent experiment. The rats were split into two groups at random in the following manner:

- **Group I** (Normal control group) (n=10): The rats were fed on a standard commercial chow diet till the end of the experimental period.
- **Group II** (Diabetic group) (n=40): Diabetic rats.
- The Diabetic rats were divided into 4 groups randomly as stated below:
- **Group IIa** (diabetic control group) (n=10): The rats fed on a combined high-fat diet (HFD) (20 g of fat/100 g of rat

chow, and 10 g glucose/ 100g of rat chow) [6].

- **Group IIb** (caloric restricted group) (n=10): diabetic rats were subjected to dietary restriction of about 50% of the food intake of the normal control group [7].
- **Group IIc** (NTX/BUP) treated group (n=10): diabetic rats were treated with NTX/BUP combination administered orally by intragastric tube in which naltrexone hydrochloride 50 mg tablet was dissolved into 50 ml distilled water then 4 ml of this suspension was administered orally by intragastric tube per kg and bupropion hydrochloride 150 mg tablet was dissolved into 15 ml distilled water then 4 ml of this suspension was administered orally by intragastric tube per kg in a ratio of 1:10 to reach a dose of 4/40 mg for 5 weeks [8].
- **Group IId** (liraglutide-treated group) (n=10): diabetic rats were treated with liraglutide. (0.3mg/kg/day, S.C) [9] for 5 weeks.

We used a commercial rat chow diet (4 kcal/g) and a lab-made formula (for each 100-g commercial diet, we add 10 g glucose (40 kcal) and 20 g (180 kcal) saturated animal fat). The following table shows the composition of the diet for all groups:

Table 1: Food composition formula for all groups.

Diet/Groups	Group I	Group II	Group IIa, IIc, IId
	Normal Control	Caloric restriction	
Calories/100 g	400 kcal	400 kcal	620 kcal
Carbohydrates	No-added glucose	No-added glucose	10% glucose
Fats	No-added fats	No-added fats	20% (Saturated animal fat)
Commercial diet	100% (500 g)	50% (250 g)	100% (500 g)

2.4 Experimental procedures

Induction of Type 2 Diabetes

Following the fifth week, rats from groups IIa, IIb, IIc, and IId, on a high-fat diet, only animals with a BMI more than 0.45 g/cm2 were considered obese, whereas animals with a BMI less than 0.45 g/cm2 were excluded. underwent an overnight fast (12 hours without food but with access to

water). This was followed by an injection of freshly made STZ solution was given intraperitoneally at a low dose of 45 mg/kg I.P., in 0.01 M citrate buffer (PH =4.5) to induce type 2 diabetes [10]. Rats were then fed 10% glucose to avoid low blood sugar. Following STZ treatment, rats were allowed unrestricted access to food and water and were maintained on their designated diets until the study was completed.

Confirmation of Type 2 Diabetes

Diabetes was randomly confirmed in certain rats in groups IIa, IIb, IIc, and IId on the 3rd day post-STZ injection through assessment of fasting serum glucose and insulin levels following an overnight fast. Rat tail vein blood samples were taken from rats that had blood glucose levels exceeding 300 mg/dL, which were categorized as diabetic rats and utilized in subsequent experiments [11].

Measurement of body weight and length

Weight was measured by using a calibrated digital scale in grams (g), and nose-to-anus length was measured in centimeter (cm). The body weights and lengths were used to calculate BMI according to the following equation: weight (g)/ Height2 (cm2) [12].

Measurement of arterial blood pressure

Blood pressure in mmHg by ADInstruments Pty Ltd. made in Australia, pI3504 model by using rodent computerized noninvasive blood pressure measurement (NIBP) CODA Monitor system [13].

Before pressure measurements started, the animals were given unrestricted access to the holder and kept there for at least ten to fifteen minutes. To stop the blood flow, an occlusion tail-cuff was put on the animal's tail. Automated measurement of mean arterial blood pressure, diastolic blood pressure, and systolic blood pressure during deflation. The average of at least four consecutive measurements was determined. BP was measured at the beginning (initial), before starting treatment (baseline diabetic), and at the end of the experimental period (final).

Scarification and Sampling

After the 10th week, after an overnight (12 hours) fast, the blood samples were delivered in heparinized capillary tubes and taken from intracardiac blood under light anesthesia with phenobarbital IP

injection, followed by cervical dislocation and delivered into centrifuge tubes and then centrifuged at 10000 RPM for 20 minutes. The serum was placed into tubes for further measurement of:

Fasting glucose level by quantitative determination.

- Fasting insulin by enzyme immunoassay using the Rat Insulin ELISA kits (Linco Research), China.
- Triglycerides (by Wahlefeld (1974) Triglyceride Quantification Kit, BioVision Research, China).
- Cholesterol (Cholesterol Assay Kit, BioAssay Systems, China).
- HDL-C (HDL-Cholesterol (mg/dl) Assay Kit, Roche/Hitachi Modular P Chemistry Analyzer, China).
- LDL-C (calculation) LDL-C (mg/dL) was determined by Friedewald's formula as follows: LDL-C = (TC) - (HDL-C) - (TG/5) [14].
- Atherogenic indices (calculations): utilizing the formulas listed below [15].
- AIP, or the atherogenic index of plasma, is equal to log (TG/HDL-C).
- Total cholesterol divided by HDL-C is Castelli's Risk Index I (CRI-I).
- LDL-C divided by HDL-C is Castelli's Risk Index II (CRI-II).
- Total cholesterol minus HDL-C = (Atherogenic coefficient (AC)) / HDL-C.

2.5 Statistical methods

The data was coded and inputted using SPSS version 28 by IBM Corp. in Armonk, NY, USA. Data was summarized using mean and standard deviation. Comparisons between groups were done using analysis of variance (ANOVA) with multiple comparisons post hoc test in normally distributed quantitative variables, while non-parametric Kruskal-Wallis test and Mann-Whitney test were used for non-normally distributed quantitative variables. P-values less than 0.05 were considered statistically significant [16].

3. Results

Table 2 shows that the fasting glucose level of the diabetic group was significantly increased compared to the control group (p <0.05), while the fasting

glucose level of the caloric restriction (NTX+BUP) and liraglutide groups was insignificantly decreased compared to the diabetic group (p <0.05). The fasting insulin level of the diabetic group was insignificantly decreased (p >0.05) and insignificantly increased in caloric restricted (NTX+BUP) and liraglutide groups compared to the diabetic group (p >0.05).

Table 2: Mean values and standard deviations of fasting serum glucose (mg/dl) and fasting serum insulin (miU/L) of all groups.

	Normal control (I)	Diabetic control (IIa)	Caloric restricted (IIb)	(NTX+BUP) treated (IIc)	Liraglutide-treated (IId)
Fasting glucose	114.71 ±17.27	650.44 ±66.32 *	276.18 ±110.87*#	287.65 ±108.17*#	295.48±102.13*#
Fasting insulin	3.57 ±1.42	2.96 ±0.84	3.25 ±0.69	4.15 ±1.43	3.5 ±1.37

**: statistically significant compared to the normal control group (p <0.05). #: statistically significant compared to diabetic control group (p <0.05).*

Figure 1 shows that the final SBP was significantly lower in the caloric restricted (NTX+BUP) and liraglutide groups when compared to the diabetic control group (p <0.05).

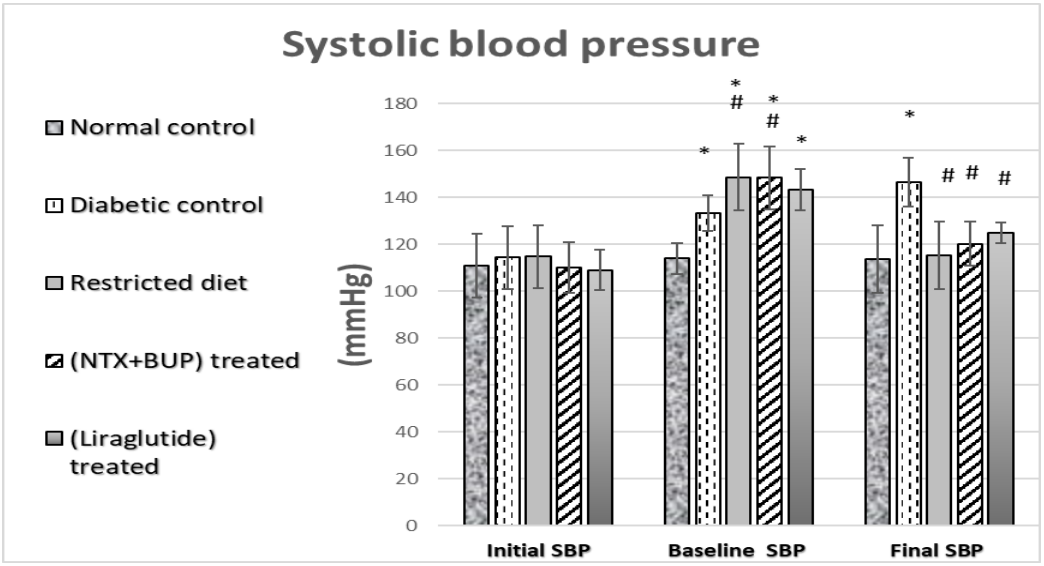

Figure 1: Mean values of SBP in (mmHg) in all studied groups at start (initial), after induction of T2DM (baseline diabetic) and at the end of the experiment (final).

Figure 2 showed that the ultimate DBP was not significantly reduced in the caloric restricted (NTX+BUP) and liraglutide groups in comparison to the diabetic control group (p >0.05).

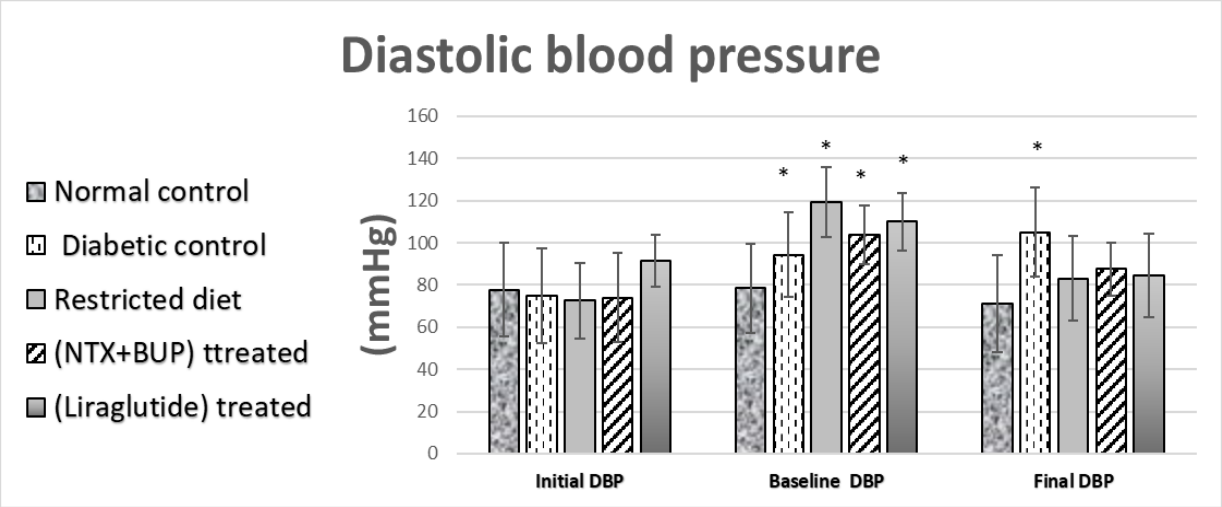

Figure 2: Mean values of DBP in (mmHg) in all studied groups at the start (initial), after induction of T2DM (baseline diabetic), and at the end of the experiment (final).

Figure 3 shows a notable reduction in final Mean Arterial Pressure in groups with caloric restriction and liraglutide (p <0.05), while there was no significant difference in the (NTX=BUP) group compared to the diabetic control group (p >0.05).

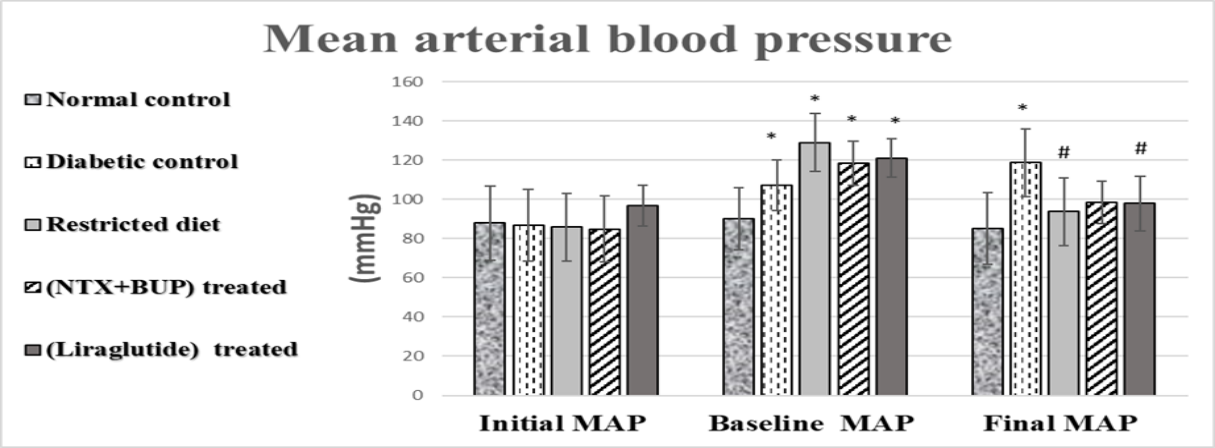

Figure 3: Mean values of MAP in (mmHg) in all studied groups at the start (initial), after induction of T2DM (baseline diabetic), and at the end of the experiment (final).

Figure 4 demonstrated that total cholesterol and LDL-c were significantly decreased in caloric-restricted (NTX+BUP) and liraglutide groups (p <0.05). Triglyceride was significantly decreased in the (NTX+BUP) and liraglutide groups. HDL-C was insignificantly decreased in caloric-restricted (NTX+BUP) and liraglutide groups (p >0.05).

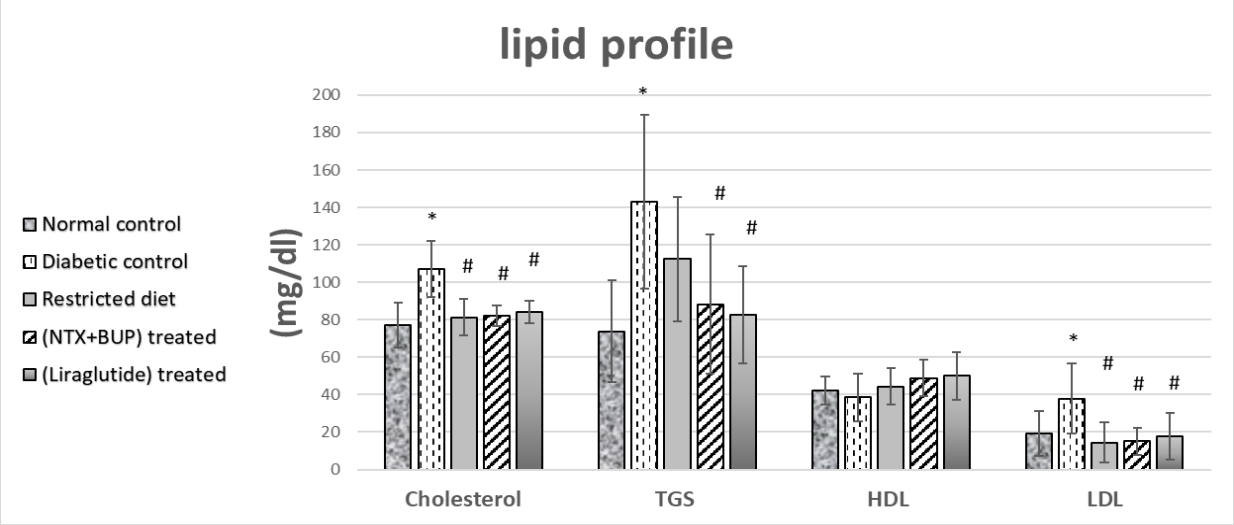

Figure 4: Mean values of serum lipid profile (Total Cholesterol, triglycerides, HDL-C, and LDL-C levels) in all studied groups.

Figure 5 demonstrated that the AIP in both the (NTX+BUP) and liraglutide groups was notably reduced, while it was only insignificantly reduced in the caloric-restricted group when compared to the diabetic group (p >0.05). CRI I, CRI II, and AC were notably reduced in the caloric restricted (NTX=BUP) and liraglutide groups when compared to the diabetic group (p <0.05).

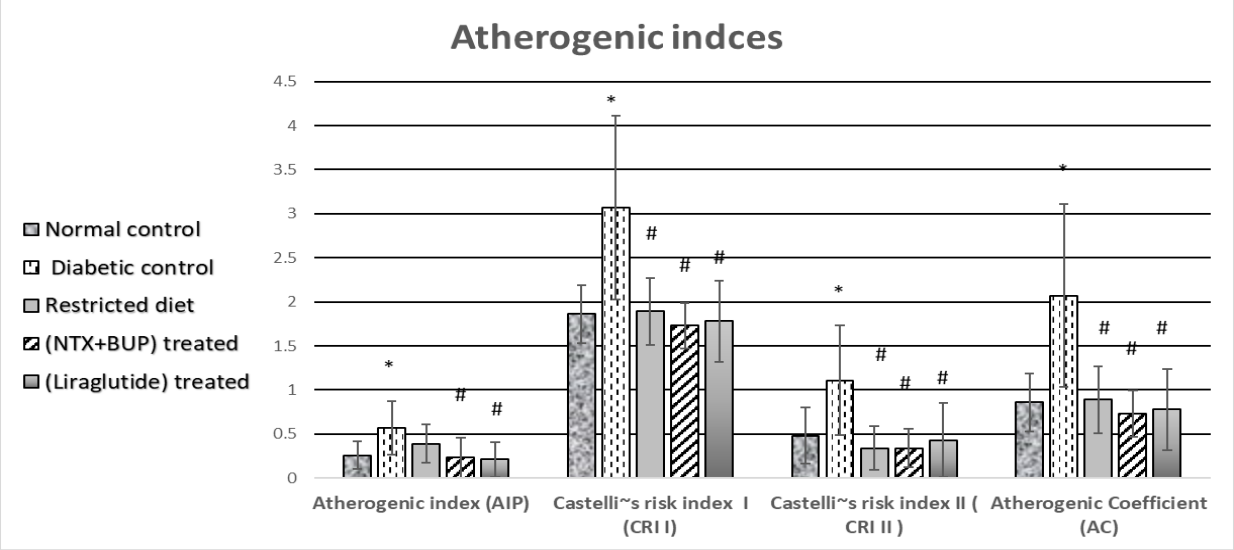

Figure 5: Mean values of AIP, CRI I, CRI II, and AC in all studied groups at the end of the experiment.

Figure 6 demonstrates a statistically significant positive correlation between the final MAP and AIP, with a correlation coefficient of 0.355 (p =0.012).

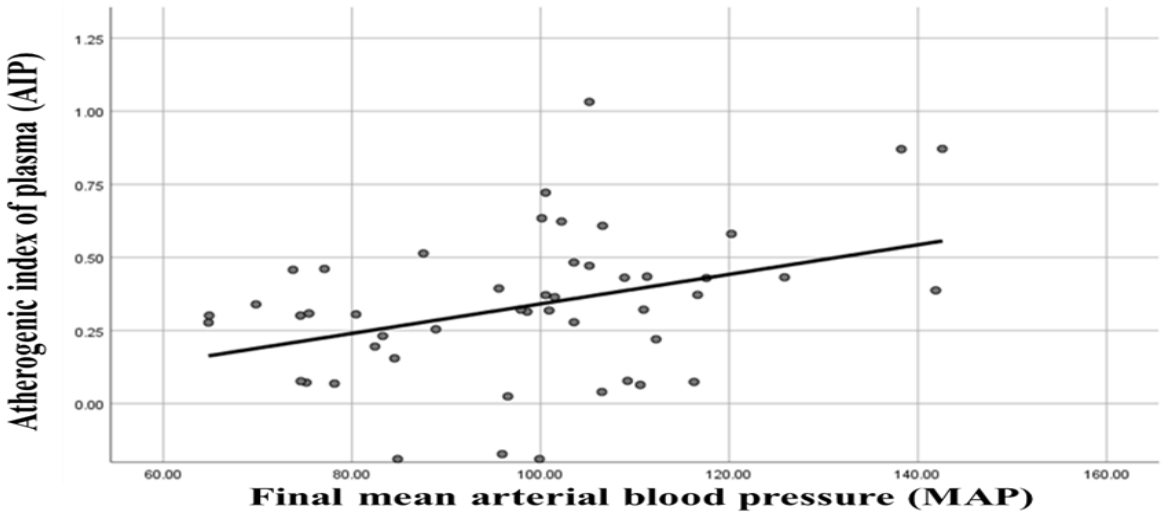

Figure 6: Correlation between final MAP and AIP.

4. Discussion

In the present study, the lipid profile and atherogenic indices of the diabetic control group compared to the normal control group showed a significant increase in serum total cholesterol, TG, and LDL-C. But HDL-C level was insignificantly decreased. In line with a study that mentioned that there was a significant increase in total cholesterol, TGs, and LDL-C, but HDL-C was insignificantly decreased in T2DM [17]. The possible mechanism of this was explained by [18], who stated that there was an increase in the production of very low-density lipoprotein (VLDL) by the liver in response to elevations in free fatty acids (FFA).

The lipid profile result in the diabetic group was supported by a significant increase in the atherogenic index of plasma, CRI I, CRI II, and atherogenic coefficient (AC). In line with a study that mentioned that AIP was significantly increased in type 2 diabetic patients [19]. In addition, the lipid profile result in the diabetic group was matched with a significant increase in systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial blood pressure (MAP). This agreed with a study that reported that diabetes significantly increased SBP, DBP [20], and MAP [21]. This was previously explained in a previous study reported that elevated non-

HDL-C was related to the incidence of high systolic and diastolic blood pressure [22].

In this study, the lipid profile and atherogenic indices of caloric-restricted groups in comparison to the diabetic group showed a notable reduction in CRI I, CRI II, and AC, while AIP showed a minimal decrease. This was explained as caloric restriction substantially reduced atherosclerosis in experimental mice by inhibiting the expression of inflammatory mediators [23]. In addition, the atherogenic indices results of the caloric-restricted group in our study were supported by a significant decrease in SBP and MAP and an insignificant decrease in DBP. This was explained as caloric restriction resulted in an improvement in endothelial function and decreased metabolic and inflammatory parameters [24].

The lipid profile of the (NTX+BUP) treated group showed a significant decrease in total cholesterol, triglyceride levels, and LDL-C levels and an insignificant increase in HDL-C. Also, this group showed a significant decrease in AIP, CRI I, CRI II, and AC.

Lipid profile and atherogenic indices results of the (NTX+BUP) treated group were matched with a significant decrease in SBP and an insignificant decrease in both DBP and MAP. In line with a previous study found that individuals treated with both (NTX+BUP) and placebo exhibited decreases in systolic and diastolic blood pressure from baseline diabetes that were numerically notable yet not statistically significant [25].

Moreover, a previous study found that treatment with naltrexone/bupropion led to a reduction in binge eating disorders in adult patients with obesity [26], and another study stated that binge eating disorders were associated with higher levels of lipid profile [27]. So, we can suppose that (NTX+BUP) treatment improves atherogenic indices by reducing binging eating disorders.

In the current study, the lipid profile of the liraglutide-treated group showed a significant decrease in serum total cholesterol, TG, and LDL-C levels and an insignificant increase in HDL-C. Also, this group demonstrated a notable reduction in AIP, CRI I, CRI II, and AC in comparison to the diabetic control group. This was clarified by a study that claimed that liraglutide, regardless of glucose levels, decreases endothelial vascular cell adhesion molecule-1 in murine atherosclerosis [28].

Furthermore, the atherogenic indices results of the liraglutide-treated group were supported by a significant decrease in SBP and MAP and an insignificant decrease in DBP. This was clarified by a study that found that a substantial reduction in body weight and an improvement in metabolic management may contribute to a notable drop in SBP in hypertension patients on liraglutide treatment [29].

5. Conclusion

Our study highlights the potential benefits of (NTX+BUP) and liraglutide in blood pressure reduction and improving atherogenic indices and lipid profile, suggesting further preclinical investigations to confirm the current results.

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Conflicts of Interest: None declared

AI declaration statement: None declared.

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