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L-arginine mitigates cardiac lipid and glucose accumulation through leptin modulation and enhancement of PIK3 activities in high fat-fed male Wistar rats

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Abstract

Background and aim Insulin resistance and other metabolic risk factors are associated with increased cardiovascular diseases in animals fed with high fat diets (HFD). L-arginine is a semi-essential amino acid produced both endogenously and taken in the diet as supplements. It has been documented to possess antioxidant and anti-inflammatory properties and has been considered a plausible candidate for the management of metabolic disorders. Therefore, this study is aimed to determine the effects of L-arginine on lipid dysregulation and insulin resistance in high fat-fed male Wistar rats.

Methods and results Twenty-four (24) male Wistar rats randomly selected into 4 groups, mean weight 110 ± 5 and, (n=6) were fed rat chow + distilled water (vehicle); CTR, rat chow + L-arginine (150 mg/kg), HFD + vehicle, HFD + L-Arginine (150 mg/kg) for 6 weeks. The animals were anesthetized with 50 mg/kg pentobarbital sodium intra-peritoneally, blood sample was taken via cardiac puncture and thereafter collected into a heparinized tube. Data were expressed as means $\pm$ SEM. HFD increased body weight gain, serum Insulin, Homeostasis model assessment of insulin resistance (HOMA-IR), area under the curve (AUC), leptin, Lipoprotein(a) or Lp(a), triglyceride-glucose index (TYG), triglycerides (TG), free fatty acids (FFAs), total cholesterol (TC), low density lipoprotein (LDL-C), TC/HDL-C, Log TG/HDL-C, TC-HDL-C/HDL-C but decreased phosphoinositide-3-kinase (PIK3) when compared with control. L-arginine, resulted in significant reduction in weight gain, fasting blood sugar (FBS), insulin, AUC, HOMA-IR, leptin, while increasing PIK3, Lp(a), TG, TC and FFA when compared with HFD.

Conclusion The amelioration of lipid and glucose accumulation by L-arginine supplementation in high fat diet-fed male Wistar rats is accompanied by reduced leptin levels and PIK3 augmentation.

Keywords Atherogenic markers, Insulin resistance, L-Arginine, Leptin, Phosphoinositide 3-kinase

Introduction

There is evidence from several studies that a high-fat diet leads to obesity and a dysregulated lipid profile with increased LDL-c and reduced HDL-c, increased circulating free fatty acids, and atherosclerotic activities [1, 2]. A study, however, showed that saturated fatty acids are the culprit in the genesis of dyslipidemia caused by a high-fat diet [3]. The mechanisms involved in HFD-induced

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obesity and dyslipidemia are complex. In order to simplify the process, it is good to consider the glucoregulatory and lipo-regulatory mechanisms that are directly or indirectly affected by HFD. Among these are the insulin and leptin pathways.

L-arginine is an amino acid known to possess antioxidant and anti-inflammatory properties that is beginning to find relevance in the management of metabolic disorders. Apart from its endogenous secretion, many food sources such as fish, red meat, dairy, eggs, pumpkin seeds, soybeans, lentils, and chickpeas are rich in L-arginine [4, 5]. In a study carried out for 12 weeks on patients with metabolic syndrome, supplementation with 5 g/day of L-arginine reduced fasting blood glucose, circulating triglycerides, and the total cholesterol to high density lipoprotein cholesterol ratio (TC/HDL-c) [6]. The benefits of L-arginine on cardiac, hepatic, pancreatic, and inflammatory obesity-related alterations in high fat diet-fed rats have been studied by Alam et al. [7] and it was found that L-arginine supplementation suppressed derangement in the left ventricle, improved the functions and structure of the liver, glucose tolerance, and blood pressure. However, the mechanisms by which L-arginine regulates glucose and lipid balance are not clear [8]. Nevertheless, lipid homeostasis is found to be significantly affected by diets and endogenous factors.

The hormone leptin is predominantly produced from adipose tissues, and its primary function is to regulate adiposity. Leptin regulates energy balance by inhibiting hunger in the hypothalamus, which in turn reduces food intake (including fat), leading to a reduction in adiposity [9]. Whereas, insulin, which is arguably the most important anabolic hormone in the body [10], regulates fats, carbohydrates, and protein metabolism. It controls the deposition of glucose into the adipocytes, myocytes, and hepatocytes from the blood [11]. A study showed that chronic HFD caused hyperleptinemia, which was associated with visceral fat accumulation [12]. Another study established that hyperleptinemia occurs at the third stage of the impact of HFD due to leptin resistance [13]. In leptin resistance, sensitivity to the hormone has drastically reduced, leading to hyperphagia despite high levels of the hormone in circulation. Several studies have linked chronic ingestion of HFD with its deleterious consequences to insulin resistance [14, 15]. Insulin resistance leads to hyperinsulinemia and associated lipid dysregulation as a result of adipose and hepatic insulin resistance, which are characterized by increased lipolysis and de novo lipogenesis respectively [16]. More precisely, among the diverse mechanisms of insulin resistance, down-regulation of phosphoinositide-3-kinase (PIK3) is very important.

Although diseases engendered by HFD are preventable, the prevalence of obesity-related diseases worldwide is alarming. It is therefore expedient that management or treatment measures with fewer adverse effects be developed. Hence, the aim of the present study was to investigate the effect of L-arginine supplementation on lipid dysregulation and insulin resistance in HFD-fed male Wistar rats.

Materials and methods

Study design, and grouping

Animals

Twenty-four (24) male Wistar rats, aged 4–5 weeks and weighing between 100 and 115 g were housed in separate cages and kept at constant environmental conditions of temperature (22–26 °C), relative humidity (50–60%) and 12-h dark/light cycle. The rats were fed on a constant ration, and fresh, clean drinking water was supplied. All the rats were also acclimatized for a period of one week prior to the commencement of the study. The study was carried out in accordance with the world accepted best practices as written in the European Commission guidelines (Directives of 2010/63/EU as amended by Regulation (EU) 2019/1010) as well as the Animal Research Reporting of In Vivo Experiments (ARRIVE) guidelines and was approved by the Ethical Review Committee, University of Ilorin, Ilorin, Nigeria (UERC/ASN/2018/357).

Chemicals

All the chemicals were of analytical grade. The chemicals used in the study include L-arginine, which was purchased from Bridge Biotech Laboratory, Ilorin, Kwara State. The L-arginine was dissolved in distilled water. It was prepared freshly and administered orally at a dose of 150 mg/kg body weight [17] for a period of 6 weeks (42 days).

High fat diet

A special high fat feed was formulated using the composition provided by Abdul Kadir et al. [18]. The high fat diet contains 414.0 kcal/100 g with 43% as carbohydrate, 17% as protein, and 40% as fat. The diet consists of 17,000 g of powdered rat feed, 1500 g of maize oil, 1500 g of ghee, and 5000 g of milk powder, giving a total of 25,000 g (25 kg) of high fat feed. The composition table is shown in (Table 1).

Animal grouping

After acclimatization to the laboratory conditions, the animals were randomly divided into four groups of six rats, placed in individual cages, and classified as follows; Control (CTR), rats received normal rat chow and 0.5 ml of distilled water daily, high fat diet-fed (HFD),

Table 1 Composition of high fat diet and normal rat chow diet

	High fat diet (%/100 g)	Normal chow (%/100 g)	% of total (25 kg)
Carbohydrate	43	48.8	
Protein	17	21	
Fat	40	3	
Calcium		0.8	
Phosphorus		0.4	
Fiber		5	
Ash		8	
Powdered rat chow			17,000
Maize oil			1500
Ghee			1500
Milk powder			5000
Powdered rat chow			17,000

rats received high fat feed only, high-fat diet and arginine (HFD + ARG), rats received a high fat diet and 150 mg/kg arginine orally, and arginine only (ARG), rats received a high fat diet and 150 mg/kg arginine orally, all for 6 weeks [18].

Collection of blood sample

After 6 weeks of treatment, animals were anesthetized with 0.8 mg Pentobarbital sodium intraperitoneally (50 mg/kg ip) and blood was collected by cardiac puncture. Blood was collected by cardiac puncture into plain tube, left for 30 min to clot in the tube and thereafter was centrifuged at 3000 rpm for 5 min at room temperature. Serum was stored frozen until needed for biochemical assay.

Fasting blood sugar test and oral glucose tolerance test (OGTT)

After 8 h of an overnight fast, the tails of the rats were pricked with a lancet blade for the FBS. Thereafter, 200 g/l of glucose in water, after proper dissolution, was given by oral gavage at a dose of 2 g/kg of body weight, and blood glucose was obtained at the tail tip at 30, 60, 90 and 120 min for glucose concentration using a handheld On-Call glucometer. This test was carried out on all rats, and the results were recorded.

Biochemical assay

Serum insulin assay

Serum insulin concentrations were measured with an enzyme-linked immunosorbent assay kit (cat number:IS130D) procured from Ray Biotechnology, Inc. (Georgia, USA). The sensitivity of the assay was

0.5 mU/L, and the inter-assay coefficients of variation were < 7.5 and 9.3%, respectively.

Homeostasis model assessment of insulin resistance (HOMA-IR)

This parameter was derived by using the formula.

$$[\text{Glucose (mmol/L)} \times \text{Insulin } (\mu\text{U/mL})] / 22.5$$

Homeostasis model assessment of beta cell (homa-beta)

This parameter was derived by using the formula.

$$\frac{360 \times \text{fasting insulin } (\mu\text{U/mL})}{(\text{fasting glucose (mg/dL)} - 63)}$$

Triglyceride-glucose (TyG) index

This parameter was derived by using the formula.

$$\text{TyG index} = \ln \left[\text{Fasting triglyceride (mg/dl)} \times \text{fasting glucose (mg/dl)} \right] / 2$$

Cardiac risk ratio

$$\text{Cardiac risk ratio} = \text{Total cholesterol (TC)} / (\text{HDL} - \text{C})$$

Atherogenic coefficient

$$\text{Atherogenic coefficient} = (\text{TC} - \text{HDL} - \text{c}) / \text{HDL} - \text{c}$$

Atherogenic index of plasma

$$\text{Atherogenic index of plasma} = \log (\text{TG} / \text{HDL} - \text{c})$$

LDL-c

$$\text{LDL} - \text{c} = \text{TC} - \text{TG} / 5 (\text{mg/dl}) [19].$$

Serum leptin assay

Serum leptin concentrations were measured by the sandwich enzyme-linked immunosorbent assay (ELISA) method on a DSX ELISA automated analyzer. Protocols were run according to the manufacturer's instructions.

The analytical sensitivity for the leptin kit was 0.7 ng/ml, specificity for human leptin was 100% and the assay dynamic range was 0.7–100 ng/ml.

Phosphotylinosital 3 kinase assay

Phosphotylinosital 3 Kinase (also known as PI3K), assay was done using the Sandwich-ELISA kit purchased from Elabscience® with Cat.NoE0438Ra.

Statistical analysis

The results were expressed as mean $\pm$ standard deviation using graph pad prism 8. The data were analyzed using one-way ANOVA. Post-hoc Tukey test was used to determine the significance of mean values among the

groups. The P -value ($P < 0.05$) was used to determine significant differences.

Results

Arginine supplementation normalized absolute body weight and attenuated percentage body weight change in rats fed with HFD

Absolute body weight was increased after the experiment compared with control in HFD-fed animals. Nevertheless, absolute body weight did not change compared with control group in animals fed arginine supplementation with or without HFD. However, HFD significantly increased the percentage body weight change compared with control ($92.1 \pm 1.1\%$ vs $25.4 \pm 0.34\%$) which was also significantly attenuated by arginine supplementation compared with HFD (Table 2).

Arginine supplementation improved insulin sensitivity in HFD-fed male Wistar rats

Fasting blood glucose, insulin and HOMA-IR were significantly raised in animals fed HFD, $P < 0.05$ (Fig. 1a, b, c).

In addition, HFD significantly reduced HOMA-B, $P < 0.05$ (Fig. 1d). Arginine supplementation in HFD-fed animals caused reduction in fasting blood glucose levels compared with HFD without supplementation. Conversely, it significantly reduced insulin, HOMA-IR, $P < 0.05$ in HFD-fed animals to levels comparable to the

Table 2 Comparison of body weight percentage (%) change between CTR, ARG, ARG + HFD

Body weight (g)	CTR	ARG	ARG+HFD	HFD
Initial	115.5 $\pm$ 2.3	105.1 $\pm$ 2.5	108.7 $\pm$ 2.1	114.5 $\pm$ 2.4
Final	144.8 $\pm$ 3.1	161.8 $\pm$ 4.1	157.2 $\pm$ 4.1	220 $\pm$ 5.1
% Change	25.4 $\pm$ 0.34	49.6 $\pm$ 0.6*	48.9 $\pm$ 0.95#	92.1 $\pm$ 1.1*

* $P < 0.05$ versus control; # $P < 0.05$ versus HFD

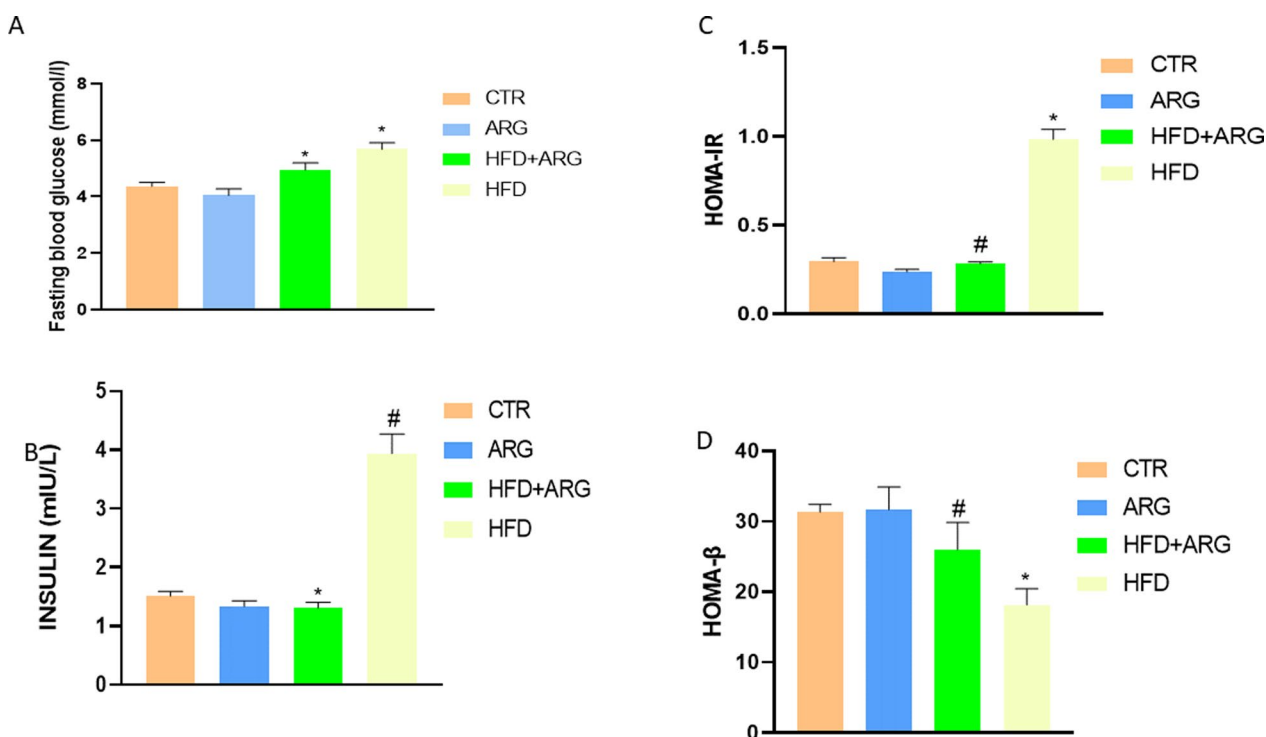


Fig. 1 Arginine (ARG) did not affect fasting blood glucose (A), but reduced insulin (B), HOMA-IR (C) and increased HOMA-β (D) in high fat diet-fed (HFD) animals. CTR: control. Data were expressed as mean $\pm$ SEM. * $P < 0.05$ versus control; # $P < 0.05$ versus HFD

control, while HOMA-B was augmented by arginine supplementation in HFD-fed animals (Fig. 1).

Arginine supplementation improved glucoregulation, attenuated leptin levels and augmented PIK3 in HFD-fed male Wistar rats

High-fat diet exposure led to a significant elevation of OGTT and AUC of OGTT, $P < 0.05$ (Fig. 2a, c).

There was also an observed increase in leptin and decrease in PIK3 levels in the HFD group compared to the control group. The arginine-treated HFD-fed group showed improvement in AUC and OGTT compared

with HFD-exposure without arginine. However, leptin level was significantly reduced and PIK3, $P < 0.05$ elevated in the HFD + arginine group compared with the HFD group (Fig. 2b, d).

Arginine normalized lipid profile in male Wistar rats fed with HFD

There was an increase in Lp(a) level and triglyceride-glucose index (TyG) in HFD-fed animals compared with control and animals exposed to only arginine (Fig. 3a, b).

The arginine-treated group that was not exposed to HFD had a normal Lp(a) level but a reduced TyG index.

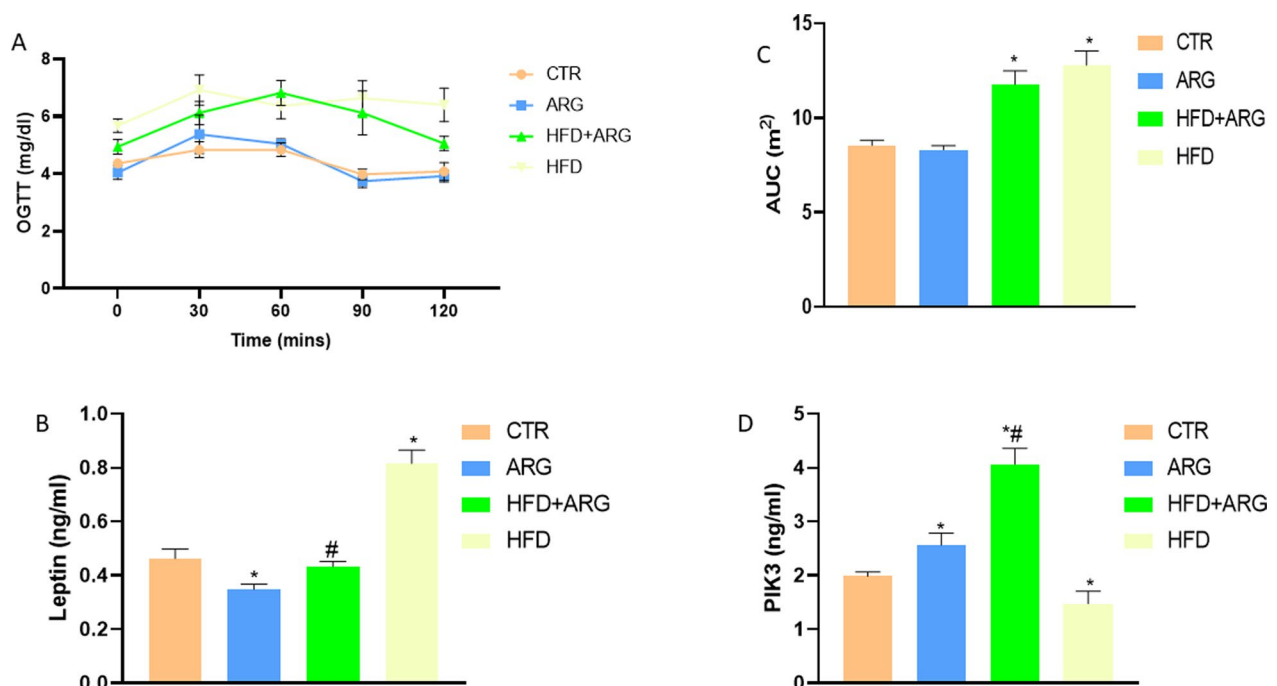


Fig. 2 Arginine (ARG) did not affect Area under the curve (AUC) of oral glucose tolerance test (OGTT) (A and C), but reduced leptin (B), and increased phosphoinositide-3-kinase (PIK3) (D) in high fat diet-fed (HFD) animals. CTR: control. Data were expressed as mean $\pm$ SEM. * $P < 0.05$ versus control; # $P < 0.05$ versus HFD

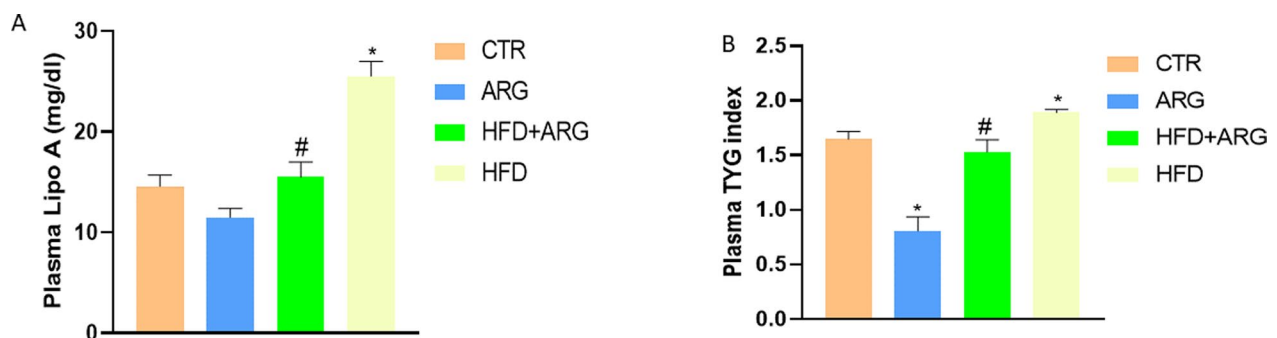


Fig. 3 Arginine (ARG) reduced lipoprotein A (Lp(a)) (A) and triglyceride-glucose index (TyG) (B) in high fat diet-fed (HFD) animals. CTR: control. Data were expressed as mean $\pm$ SEM. * $P < 0.05$ versus control; # $P < 0.05$ versus HFD

However, arginine treatment in animals exposed to HFD significantly reduced both Lp(a) level and the TyG index $P < 0.05$. High-fat diet significantly increased plasma TG, FFA, TC and LDL-C, $P < 0.05$ compared with control and animals exposed to only arginine. Arginine treatment reduced TG, FFA, TC and LDL-C in the plasma of HFD-fed male Wistar rats (Fig. 4a, b, c, d).

In addition, HDL-C was not affected by HFD compared with control, but it was significantly increased by arginine with or without HFD, $P < 0.05$ (Fig. 5a). However, plasma TC/HDL, the logarithm of TG/HDL and TC/HDL ratios were elevated in HFD-fed rats. Arginine treatment with or without HFD exposure reduced the ratios compared with both control and HFD without arginine treatment (Fig. 5b, c, d).

Discussion

The findings of the present study demonstrated that high-fat diet increased body weight gain, insulin resistance, circulating leptin, and lipids to a profound degree. In addition, the elevated circulating lipid ratios (TG/HDL and TC/HDL) in HFD-fed animals are indicative of glucose dysregulation, lipid dysregulation, and atherothrombotic conditions. Nevertheless, the elevated circulating leptin indicates leptin resistance and is associated with increased body weight gain observed in HFD-fed animals in this study. However, L-arginine administration

to HFD-fed animals reduced body weight gain, improved insulin sensitivity, and corrected dysregulation of leptin and lipids (Fig. 6). This study also demonstrated that the effects of L-arginine are accompanied by enhancement of PIK3, a molecule located downstream of the insulin receptor.

HFD-fed animals in this study had elevated body weight changes, which can be attributed to the probable fat accumulation due to chronic HFD exposure. Fat accumulation is the basis for the development of obesity and obesity-related diseases. Increase in body weight is a risk factor for metabolic syndrome and atherosclerotic diseases, and the high prevalence of metabolic diseases can be linked to increased consumption of western diets and processed foods [19]. Daily consumption of western diets and an increasingly sedentary lifestyle have caused a large increase in body weight among young adults in recent years, predisposing them to metabolic disease and atherosclerosis [20]. High fat diet exposure enhances lipotoxicity which causes metabolic derangements as a result of free fatty acid accumulation leading to insulin resistance [21]. High fat diet in this study increases Lp(a) which is an important lipoprotein contributing to atherosclerotic cardiovascular disease and this was attenuated with arginine supplementation (Fig. 3a). The association between Lp(a) and major cardiovascular disease (CVD) outcomes is highly predictive and a raised Lp(a) is a risk

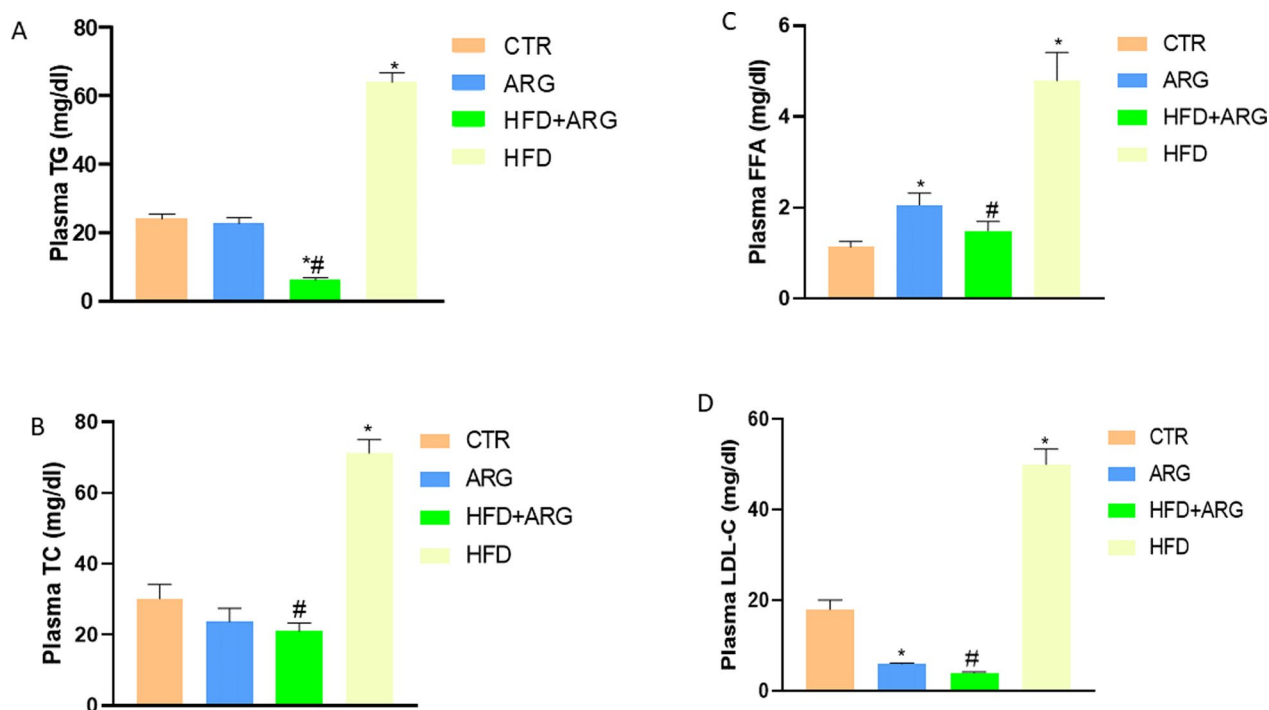


Fig. 4 Arginine (ARG) reduced plasma triglyceride (TG) (A), total cholesterol (TC) (B), free fatty acid (FFA) (C) and low-density lipoprotein-cholesterol (LDL-c) (D) in high fat diet-fed (HFD) animals. CTR: control. Data were expressed as mean ± SEM. * $P < 0.05$ versus control; # $P < 0.05$ versus HFD

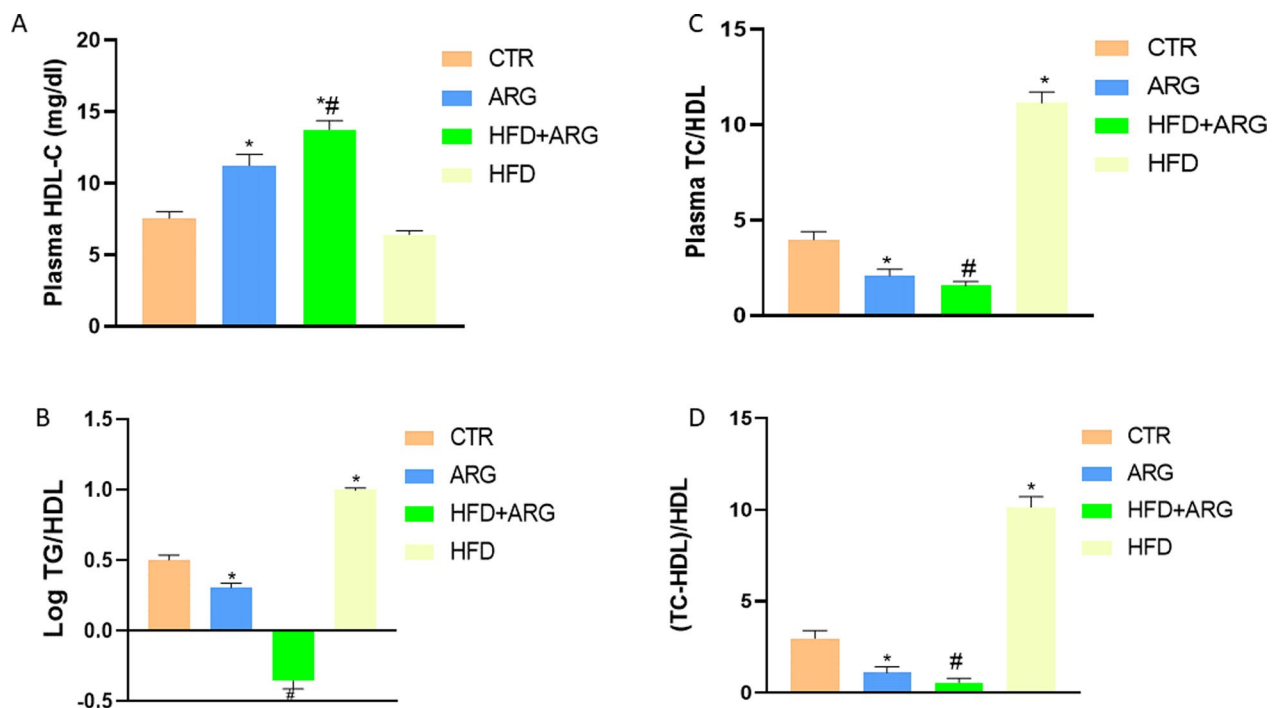


Fig. 5 Arginine (ARG) increased high density lipoprotein-cholesterol (HDL-C) (A), and reduced plasma total cholesterol/HDL ratio (B), log of triglyceride (TG)/HDL ratio (C) and atherogenic coefficient (TC-HDL)/HDL (D) in high fat diet-fed (HFD) animals. CTR: control. Data were expressed as mean $\pm$ SEM. * $P < 0.05$ versus control; # $P < 0.05$ versus HFD

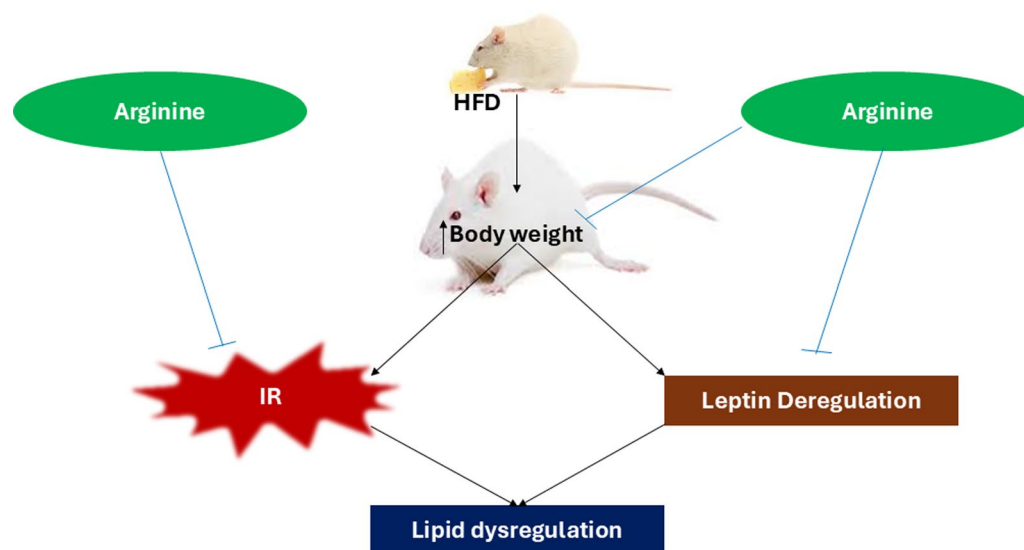


Fig. 6 Graphical abstract showing the effect of arginine on high fat diet (HFD) induced body weight gain, insulin resistance (IR), leptin deregulation

factor even at very low low-density lipoprotein (LDL-C) concentration.

From this study, HFD engendered insulin resistance (Fig. 1), elevated circulating leptin (Fig. 2B) and markers of atherosclerotic disease (Fig. 3, 4, 5). These findings are

similar to the results of other studies in which rats fed HFD [22], a high fructose diet [23] and induced with type 2 diabetes [24] showed great metabolic impairments. The mechanisms of these three common models of metabolic syndrome are diverse but related. Whereas high fructose

exposure mainly uses uric acid and related mechanisms to engender metabolic derangements, the induction of type 2 diabetes uses insulin deficiency to set up glucose dysregulation, which eventually leads to overt metabolic disease. However, HFD compromises insulin sensitivity via lipotoxicity and among the molecules that initiate insulin action, PI3K has been greatly implicated. The functions of PI3K include, but not limited to activation of protein kinase B (Akt) which initiates cell growth, cell trafficking, among others. The translocation of GLUT4 is among the actions that are engendered by PI3K which is usually the determinant step in insulin sensitivity. In this study, HFD significantly reduced PI3K levels compared to the control, meaning that the HFD-engendered derangement of insulin sensitivity is dependent on PI3K regulation. Once insulin sensitivity is compromised by HFD, the stage is set for other pathologies like leptin resistance, obesity, and atherosclerosis, which are precursors of metabolic disease complications.

Several pharmacological interventions used for management of the multifactorial metabolic diseases are usually associated with side effects and/or limitations. However, many research efforts are directed towards characterizing safe and effective treatments. One of the various considerations is dietary molecules. In this study, L-arginine, an amino acid and precursor for nitric oxide synthesis, was strategically studied for its ameliorative effect on lipid dysregulation in HFD-fed rats. It was found that L-arginine reduced weight gain and resolved the insulin resistance and leptin dysregulation associated with HFD. Nevertheless, these observations were associated with improved lipid regulation and the augmentation of PIK3. PIK3 pathways mediate the effects of insulin on vascular functions via increased nitric oxide production [25]. Enhanced vascular relaxation can increase blood flow and insulin action. Since L-arginine is a precursor of nitric oxide, increased bioavailability causes a compensatory elevated PIK3 expression through a neo-vascularization effect [26]. This elevated PIK3 increases the cells' insulin sensitivity by up-regulating insulin receptor substrate activation of PIK3.

The mechanisms of insulin resistance promote the activation of immune responses via the ERK/MAPK/NFkB pathway, especially in adipose tissues [27]. High-fat diet has been shown to induce low-grade inflammation, which produces inflammatory cytokines in adipose tissues [28]. One of the proinflammatory cytokines that interact with the immune system in adipose tissues is leptin. High-fat diet may therefore induce hyperleptinaemia via the induction of proinflammatory cytokines in the adipose tissue. An important significance of this study is the fact that chronic HFD exposure in animal models depicts rampant diet-related metabolic disease in the

western world, which is spreading wildly in low-income developing countries because of the disruptive adoption of western diets. In the present study however, arginine supplementation attenuated leptin levels in high fat diet-fed male Wistar rats. This outcome can be a pointer to the anti-inflammatory role of arginine and leptin modulation through enhanced insulin sensitivity.

Conclusion

In conclusion, L-arginine ameliorates lipid and glucose dysregulations by reducing leptin level and enhancing PIK3 signaling activities in high fat-fed male Wistar rats. Consumption of food rich in L-arginine may be of tremendous value to people suffering from metabolic disorders such as obesity and cardiovascular diseases and this can form an important component of lipid lowering agents.

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Author contributions

A.O., O.B., B.B.A. and A.M.A. conceived and designed the research. A.O.O. and B.B.A. conducted the experiments. A.O.O. and A.M.A. contributed to the new reagents and analytical kits. A.O.O., B.B.A. and A.M.A. analyzed and interpreted the data. A.O.O., B.B.A. and A.M.A. drafted the manuscript. A.O.O., B.B.A. and A.M.A. read and approved the final manuscript.

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Data availability

No datasets were generated or analysed during the current study.

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