

# Effect of L-arginine on Markers of Metabolic Syndrome Related to Abdominal Obesity and Disorder of Lipid Metabolism in Female Wistar Albino Rats

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**Abstract** Metabolic syndrome (MES) (a cluster of features indicating metabolic disorders), is associated with a significant reduction in nitric oxide, NO, a major metabolite of L-arginine (ARG). Abdominal obesity and lipid disorder are among the risk factors whereas female gender is an independent risk factor for the development of MES in animals. Therefore, the aim of this study is to ascertain the effect of ARG on markers of MES related to abdominal obesity and disorder of lipid metabolism, using female Wistar albino rats as model. Two groups of female rats were given a single dose of 3 ml/kg body weight (bw) of distilled water, DW, and 60 mg/kg bw of ARG, respectively as control and treated groups. Exposing ARG to female rats evoked a non-significant increase ( $p > 0.05$ ) in waist circumference ( $13.00 \pm 0.84$  cm) and waist:stature ratio ( $0.43 \pm 0.04$ ) but a significant increase ( $p < 0.01$ ) in triacylglycerol to high density lipoprotein cholesterol (TAG:HDL-cholesterol) ratio ( $3.46 \pm 0.06$ ) of the rats, suggesting abdominal obesity that may worsen metabolic syndrome (MES) in the animals. The exposure elicited a significant increase ( $p < 0.01$ ) in the concentration of total cholesterol (T-cholesterol) ( $69.36 \pm 0.24$  mg/100 ml), HDL-cholesterol ( $26.20 \pm 0.47$  mg/100 ml), low density lipoprotein cholesterol (LDL-cholesterol) ( $1.41 \pm 0.50$  mg/100 ml) and triacylglycerol (TAG) ( $90.77 \pm 0.13$  mg/100 ml) in the rats' serum. These indicate adverse influence on lipid metabolism, and possibly on MES related to disorder of lipid metabolism in the female rats. In conclusion, this study suggests that ARG aggravated the markers of MES related to abdominal obesity and lipid metabolism in the female rats. This negates the hoped-for potential of ARG in the management of MES in animals.

**Keywords** Metabolic Syndrome, Abdominal Obesity, Lipid Metabolism, L-Arginine, Waist:Stature Ratio

## 1. Introduction

Abdominal obesity is an important cardiovascular risk factor and was among the listed components of metabolic syndrome (MES)[1]. Abdominal obesity or high waist circumference and lipid disorder are among the risk factors for the development of MES in animals[2]. In particular, lipids are atherogenic and the deposition of plaques in the blood vessels following their increase narrows the blood vessels resulting to high blood pressure or hypertension which is a major component of MES.

Metabolic syndrome is a cluster of cardiovascular risk factors that is characterized by obesity, atherogenic dyslipidemia, and hypertension[3,2]. It is not a disease entity but a cluster of medical disorders in an individual that could predispose animals to further health challenges. The further health challenges include type 2 diabetes mellitus[4,5], cancer[6-9] and obstructive sleep apnea[10].

Therefore, MES could contribute to significant premature mortality[11]. Its scourge is pandemic, and the pattern cuts across every age, location and gender hence is of global public health concern[12,13]. However, MES is more prevalent in developed nations, urban areas, female gender and with increasing age than otherwise[14,15].

The association of a significant reduction in NO with the pathophysiology of MES[16] suggested that L-arginine (ARG), a major precursor in the synthesis of NO[17], may improve MES in animals. Obesity and lipid metabolism are linked through the activity of insulin. This is because insulin, the key hormone in the regulation of glucose homeostasis, is the main pathogenic factor of type 2 diabetes mellitus and the main feature of obesity which are major components of MES [18]. Essentially, insulin stimulates glucose transport, uptake and utilization by cells; inhibits hepatic gluconeogenesis; and decreases adipose-tissue lipolysis and hepatic production of very-low-density lipoproteins[2].

The present study aimed to ascertain the effect of ARG on markers of MES related to abdominal obesity and lipid metabolism. This study sought to achieve the stated aim through the set objectives of studying the effect of ARG on the waist circumference, waist:stature ratio and concentration of total

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cholesterol, high density lipoprotein cholesterol, low density lipoprotein cholesterol and triacylglycerol, using female rats as model. This is because these parameters are good indicators of features and risk factors of components of MES, including diabetes mellitus, cardiovascular diseases and obesity.

## 2. Materials and Methods

### 2.1. Chemicals and Reagents

The chemicals used in this study were of analytical grade and were products of reputable companies based in Europe and America.

### 2.2. Concentration Determination/Justification

The test concentration, ARG (60 mg/kg body weight, bw) was calculated and adjusted based on the WHO reported daily ARG oral intake [19] and the concentration used in earlier studies [20, 21, 22, 23].

### 2.3. Equipment/Instruments

The Department of Biochemistry, University of Nigeria, Nsukka and Bishop Shanahan Memorial Hospital, Nsukka provided standard equipment and instruments used in the course of this study. These include the following, Bench centrifuge (Wisterfuge model 1384), UV/Vis Spectrophotometer (JENWAY 6205), Spectrophotometer (NOVASPEC LKB Biochrome, model 4049, Germany).

### 2.4. Experimental Design

#### 2.4.1. Animals and Treatment

Procurement of female weanling Wistar rats used in this study was from the animal house of the Faculty of Biological Sciences University of Nigeria, Nsukka. The rats weighed 60-80 g. The animal study was according to International guidelines for the care and use of laboratory animals in Biomedical Research[24].

The rats acclimatized for a week and immediately thereafter were randomized into two groups with sample size of eight rats each. Group B rats were exposed to ARG (60 mg/kg bw) whereas Group A rats were given distilled water (DW) (3 ml/kg bw). Exposure route was by oral intubation, which was consecutive for 28 days.

The rats, housed in a well-ventilated stainless steel cages at room temperature (28±2°C) and tropical humid condition, were maintained under standard natural photoperiodic condition of twelve hours of light alternating with twelve hours of darkness. In compliance with the ethical guidelines for treating laboratory animals, the rats were allowed unrestricted access to tap water and standard rat chow (Grand Cereals and Oil Mills Limited, Jos, Nigeria) for the experimental period.

#### 2.4.2. Sample Collection and Preparation

The animals were fasted overnight before sacrifice after 28 days. Collection of the respective blood samples of animals was by ophthalmic venous plexus or retro orbital sinus venipuncture. This involved inserting a sterile capillary tube into the medial canthus of the eye of the rat to puncture the retro-bulbar plexus resulting in out flow of blood into clean non-anticoagulated glass sample tubes.

Centrifugation of clotted blood at 3000 rpm for 10 minutes yielded the serum. Thereafter, the serum (aspirated separately into stoppered polystyrene tubes) was stored in a deep freezer for subsequent use in determining the selected serum biochemical markers of metabolic syndrome (total cholesterol, high density lipoprotein cholesterol and triacylglycerol concentrations).

### 2.5. Parameters Determined

#### 2.5.1. Serum Total Cholesterol Concentration (T-Chol) Concentration

The serum total cholesterol concentration determination was by the method of Zlatkis *et al.*[25]. The method is based on the principle that the reaction of both cholesterol and cholesterol esters with ethanol and the hydrochloric acid (HCl) in chromogen could yield color of equal absorbancies measured at 550 nm.

#### 2.5.2. Serum High Density Lipoprotein Cholesterol (Hdl-Chol) Concentration

This was estimated by the method as described[26]. This method based on the principle that chylomicrons, very low density lipoprotein (VLDL) and low density lipoprotein (LDL) are precipitated by phosphotungstic acid in the presence of magnesium, leaving high density lipoprotein (HDL) in solution. The colorimetric reading was at 560 nm.

#### 2.5.3. Serum Low Density Lipoprotein Cholesterol (LDL-Chol) Concentration

Serum LDL-cholesterol estimation was from the relationship as given by Ochei and Kolhatkar[26] thus:

$$\text{LDL-cholesterol (mg/100 ml)} = \text{Total cholesterol} - (\text{HDL-cholesterol} + 0.46 \times \text{TAG}) \quad (\text{All in mg/100 ml})$$

#### 2.5.4. Serum Triacylglycerol (TAG) Concentration

The serum TAG concentration determination was by the method of Calson[27]. This method based on the principle of colorimetric determination of glycerol (at 570 nm) after alkaline hydrolysis of glycerides.

#### 2.5.5. Height (Stature) and Waist Circumference

The height and waist circumference measurements of the rats were in centimeters before conversion to metres. The height was measured from nose slit to tail and the waist: stature ratio computed.

## 3. Statistical Analysis

Analysis of data to determine the significant differences in means was by Student's t-test, using the Statistical Package for the Social Sciences (SPSS) for Windows version 16.0 (SPSS Inc., Chicago, IL., USA). Results were expressed as mean and standard deviation (Mean $\pm$ SD) of eight rats per group at significance level of  $p < 0.01$ .

## 4. Results

### 4.1. Waist Circumference

The results of the present study reveal that rats exposed to ARG (Group B) had a non-significant ( $p > 0.05$ ) increase ( $13.00 \pm 0.84$  cm) in their measured waist circumference relative to the control ( $12.75 \pm 0.71$  cm) (Figure 1). The results show that the waist circumference of rats increased by only 1.96% in ARG-fed rats relative to the control.

### 4.2. Waist: Stature Ratio

The waist:stature ratio increased in the ARG-treated rats ( $0.43 \pm 0.04$ ) in contrast with the control ( $0.42 \pm 0.03$ ). The observed increase (2.38%) in ARG-treated group relative to the control however was not statistically significant at 0.05 probability level (Figure 2).

### 4.3. Serum Total Cholesterol (T-Chol) Concentration

The serum T-chol concentration increased in rats given ARG ( $69.36 \pm 0.24$  mg/100 ml) when compared with control ( $42.37 \pm 0.18$  mg/100 ml). The observation (representing an increase of 63.70 %) was statistically significant at 0.01 probability level (Figure 3).

### 4.4. Serum High Density Lipoprotein Cholesterol (HDL-Chol) Concentration

The results of the present study as presented in Figure 4 reveal that the serum HDL-chol concentration increased in rats that were fed ARG ( $26.20 \pm 0.47$  mg/100 ml) as against the control ( $24.47 \pm 0.73$  mg/100 ml). The observed difference (representing an increase of 7.07 %) was statistically significant at 0.01 probability level.

### 4.5. Serum Low Density Lipoprotein Cholesterol (LDL-Chol) Concentration

A significant elevation ( $p < 0.01$ ) in serum LDL-chol concentration ( $1.41 \pm 0.50$  mg/100 ml) was observed in the ARG-fed rats compared with the control rats ( $0.57 \pm 0.51$  mg/100 ml). The increase in serum LDL-chol concentration observed in ARG-fed rats is 147.37 % relative to the control (Figure 5).

### 4.6. Serum Triacylglycerol (TAG) Concentration

The serum TAG concentration results of this study, as depicted in Figure 6, increased in ARG-treated animals ( $90.77 \pm 0.13$  mg/100 ml) compared with the control ( $39.60 \pm 0.77$  mg/100 ml). The observation was statistically signifi-

cant at 0.01 probability level and represented an over one-fold increase (129.22 %) relative to the control.

### 4.7. Serum Triacylglycerol to High Density Lipoprotein Cholesterol (TAG: HDL-Chol) Ratio

The results of the present study as shown in Figure 7 reveal that the serum TAG: HDL-chol ratio of the ARG-treated rats ( $3.46 \pm 0.06$ ) increased ( $p < 0.01$ ) above that of the control rats ( $1.62 \pm 0.06$ ). This is an over one fold (113.58 %) increase relative to the control.

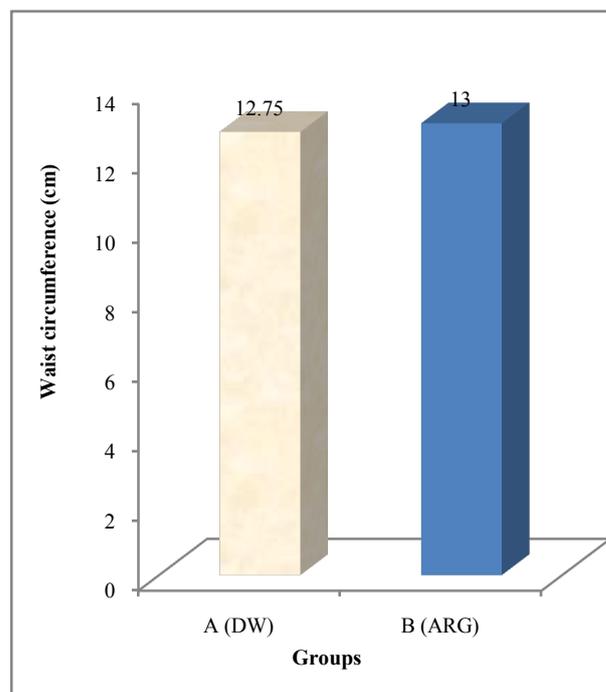


Figure 1. Influence of DW and ARG on Waist circumference of rats

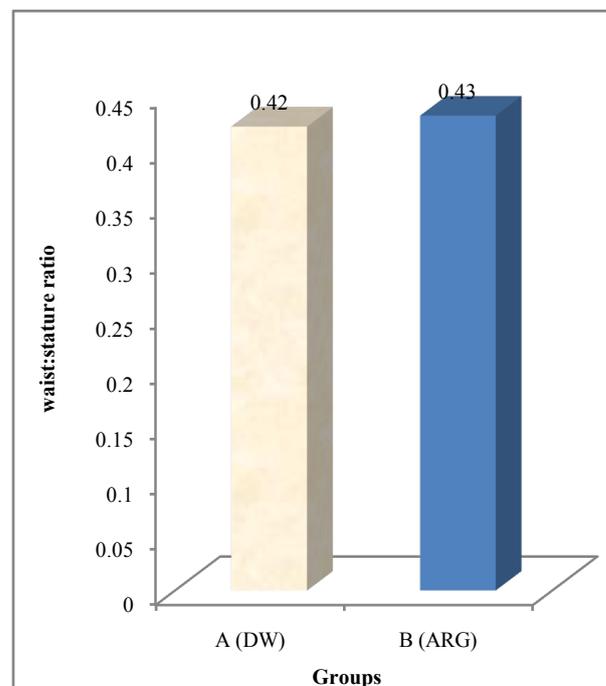


Figure 2. Effect of DW and ARG on Waist:Stature ratio of rats

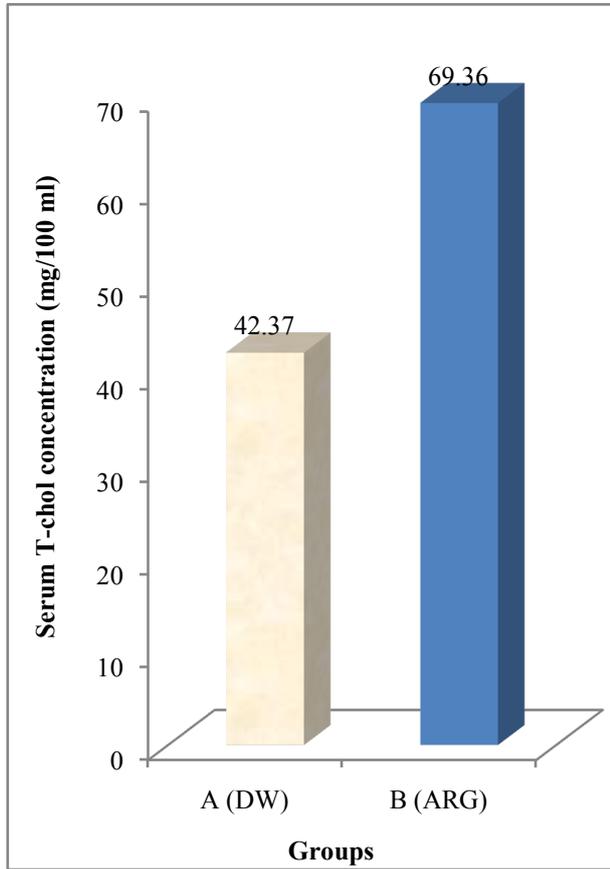


Figure 3. Effect of DW and ARG on serum T-cholesterol concentration of rats

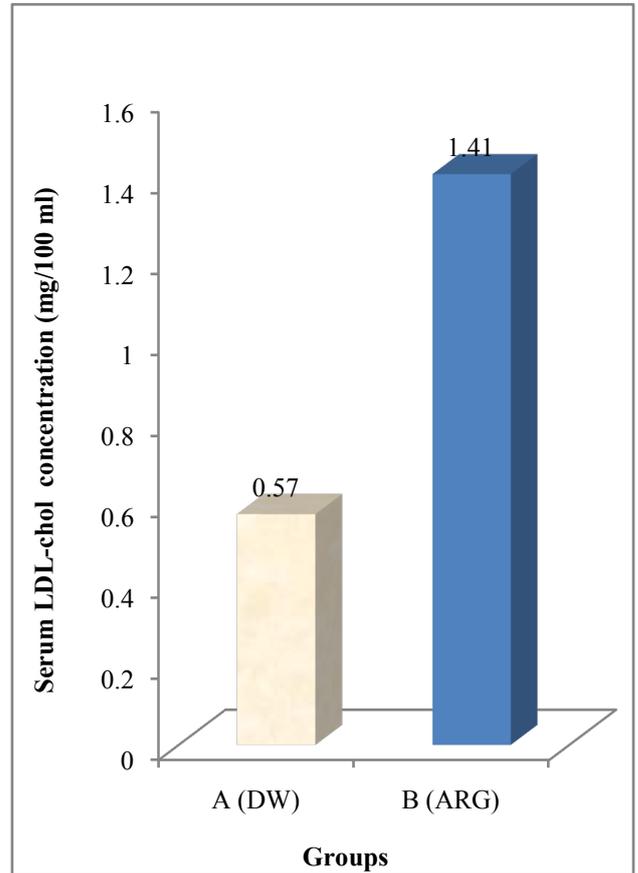


Figure 5. Effect of DW and ARG on LDL-cholesterol concentration of rats

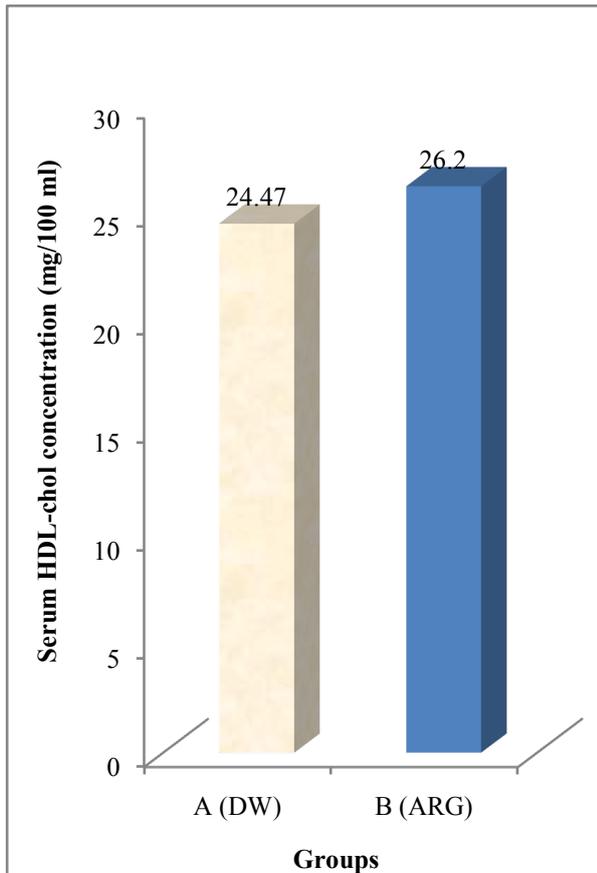


Figure 4. Effect of DW and ARG on HDL-cholesterol concentration of rats

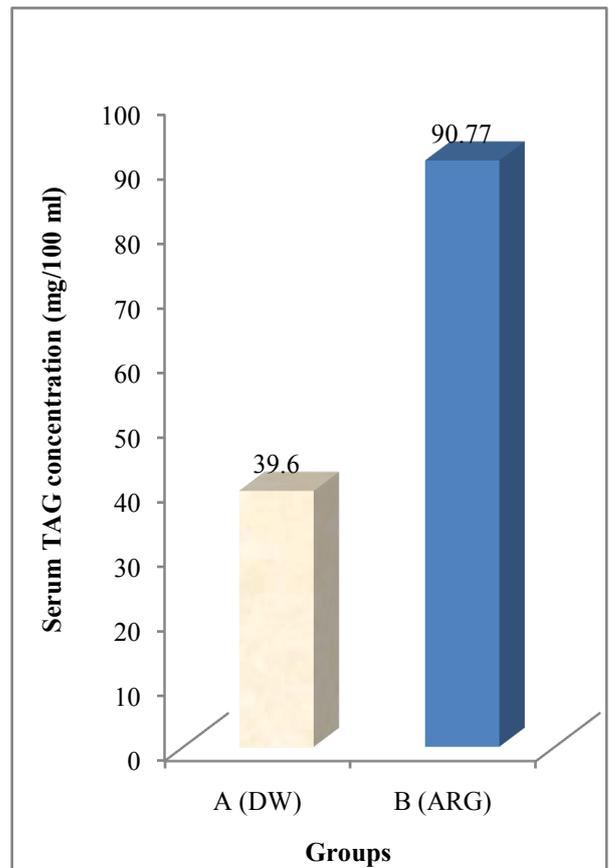


Figure 6. Effect of DW and ARG on TAG concentration of rats

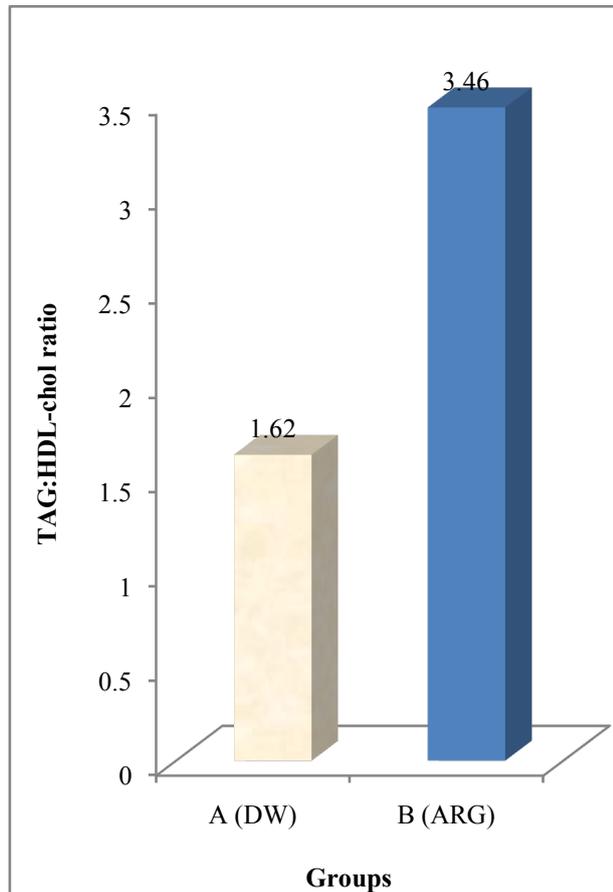


Figure 7. Effect of DW and ARG on serum TAG:HDL-cholesterol ratio of rats

## 5. Discussion

Abdominal obesity or high waist circumference and lipid disorder are among the risk factors for the development of metabolic syndrome (MES) in animals[2]. Following the association of a significant reduction in nitric oxide with the pathophysiology of MES[16], it was speculated that L-arginine, a major precursor in the synthesis of NO, may improve MES in animals[28]. This study therefore, aimed to ascertain the effect of ARG on markers of MES related to abdominal obesity and lipid metabolism.

Waist circumference and waist:stature ratio increased in ARG group, reflecting insulin resistance[29], increased adiposity[30] or incidence of MES[31]. In particular, increased waist:stature ratio (a marker of abdominal obesity) was associated with cardiovascular diseases[32], type 2 diabetes mellitus[33,34] and MES[35,36]. In apparent support of this finding, TAG:HDL-cholesterol ratio, another marker of abdominal obesity[1] increased in ARG-fed rats. Thus, ARG may worsen MES related to increased abdominal obesity in the female rats.

Increase in T-cholesterol concentration occurred in diabetes mellitus and heart diseases[26]. Thus, lowering serum total cholesterol prevented cardiovascular disease[37] a major risk factor for MES in animals. In this study, exposure of the female rats to ARG increased ( $p < 0.01$ ) T-cholesterol concentration

in the rats' serum, suggesting adverse influence on cholesterol metabolism and possibly MES related to abnormal cholesterol metabolism in the rats. Thus, ARG may worsen increased T-cholesterol contribution to MES in the female animals.

Furthermore, the ARG-induced increase ( $p < 0.01$ ) in serum LDL-cholesterol concentration in this study underscores adverse response on MES associated with compromised cholesterol metabolism in the animals, perhaps resulting from cardiovascular risks[38]. Low density lipoproteins play a key, but adverse, role in cholesterol transfer and metabolism[39] by carrying the circulating cholesterol from the liver to the peripheral tissues[26]. LDL-cholesterol is therefore atherogenic[40]; hence it is a risk factor for cardiovascular disease[41] by increasing triacylglycerol production *via* enhanced fatty acid accumulation in adipocytes[42]. Thus, ARG may worsen increased LDL-cholesterol contribution to MES in female animals.

Consistent with the present result on LDL-cholesterol concentration, data reveal that exposure of the rats to ARG increased ( $p < 0.01$ ) triacylglycerol (TAG) concentration in the rats' serum, indicating possible MES feature[43,2,15]. Increased TAG concentration was a risk factor for arteriosclerosis[26], and possibly MES. Thus, exposing the female rats to ARG may aggravate MES related to their increased TAG concentration.

Exposing ARG to the female rats had a significant increase ( $p < 0.01$ ) on the serum high density lipoprotein cholesterol (HDL-cholesterol) concentration of the rats. This could be reflective of protective influence on MES in the rats. Increasing HDL-cholesterol protected against the development of cardiovascular disease[37,43,2], possibly by transporting cholesterol from the peripheral tissues back to the liver[26]. Thus, ingesting ARG by rats may improve MES related to an increase in HDL-cholesterol.

Generally, lipid disorder is a major risk factor for the development of MES in animals. Lipids are atherogenic and the deposition of plaques in the blood vessels following their increase narrows the blood vessels resulting to high blood pressure or hypertension which is a major component of MES. However, the apparent ARG-induced benefit on MES related to HDL-cholesterol metabolism may not be significant considering the observed ARG-induced adverse influence on other MES parameters related to lipid metabolism of the rats. Thus, exposure of the rats to ARG may elicit much adverse influence on lipid metabolism that may worsen MES hence it is not advisable to use ARG in the management of MES related to impaired lipid metabolism in female rats.

In conclusion, these data suggest that ARG may worsen MES probably by eliciting adverse influence on abdominal obesity and lipid metabolism as indicated by the apparent ARG-induced adverse influence on the studied markers of abdominal obesity and lipid metabolism in the female rats. This may negate the hoped-for potential of ARG in the management of MES in animals; hence further studies in this direction are needed for corroboration or otherwise.

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