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RESEARCH ARTICLE

Diet-induced obesity influences atherogenic indices and increases risk of cardiovascular disease in male Wistar rats

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Abstract

Background: Relationship between obesity and cardiovascular diseases is complex. This study aimed to evaluate the correlation between diet-induced obesity and atherogenic indices. **Material and methods:** Two groups of 8-weeks old male Wistar rats (170 ± 15 g) were fed with normal chow and high fat diet (HFD) respectively ad libitum for 10 weeks. Body mass index (BMI), adiposity index, serum lipid profile and atherogenic indices were measured. Associations between lipidemic indices, BMI and atherogenic indices were evaluated. **Results:** The group fed with HFD only had significantly increased BMI (0.7630 ± 0.083, $p = 0.0065$). Serum TG ($p < 0.01$), LDL-c ($p = 0.017$), VLDL-c ($p < 0.01$), and total cholesterol ($p = 0.035$) were significantly elevated among the animals with relatively higher BMI (BMI > 0.0.71 g/cm2). There was a significant positive linear association of BMI with most of the atherogenic indices investigated: coronary risk ratio (CRR) (OR 48; 95% CI 4.993, 461.50; $p < 0.001$), atherogenic index (AI) (OR 1.0; 95% CI = 2.56, 229.57; $p < 0.001$) and atherogenic coefficient (AC) (OR 65.0; 95% CI 6.68, 648.26; $p < 0.001$). **Conclusions:** Consumption of HFD induces hyperlipidemia and increase the risk of coronary artery diseases by increasing the atherogenic indices.

Keywords: obesity · dyslipidemia · high fat diet · atherogenic index · coronary risk ratio

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Introduction

Inferring from the World Health Organization report (2016), there are about 2 billion overweight adults globally. Of these, over 650 million adults were obese (body mass index, BMI ≥ 30). In 2016, 39% of adults ≥ 18 years (39% of men and 40% of women) were overweight. Overall, about 13% of the world's adult population (11% of men and 15% of women) was obese in 2016. The worldwide prevalence of obesity nearly tripled over the last five decades [1]. Obesity causes poor health outcomes, reduces quality of life [2], reduces socio-economic productivity and cost nations about 0.7-2.8% of their GDP annually [3]. These staggering statistics presents obesity as a serious global threat that deserves urgent attention.

The principal cause of obesity is due to an organism's inability to physiologically maintain energy balance in the long term. This may result from over-dependence on high calorie diet, low caloric expenditure, and idiopathic inhibition of substrate oxidation [4]. It substantially increases the risk of myocardial infarction, stroke, and chronic illnesses such as type 2 diabetes mellitus, fatty liver disease, hypertension, dementia, osteoarthritis, obstructive sleep apnea and several cancers [5]. Dyslipidemia occurs early in obesity and becomes marked as the patient advances into the morbid stage of obesity either with or without insulin resistance [6]. This is associated with a relative increase in the levels of pro-atherogenic lipids (triglycerides (TGs) and low density lipoprotein (LDL-C)) as opposed to levels of anti-atherogenic lipids (high density lipoprotein – HDL-C). This phenotypic imbalance in plasma lipid distribution is strongly correlated to increased visceral adiposity, increased inflammation (systemic and vascular) increased risk of atherosclerosis (via vascular endothelial dysfunction), plaque formation, and increased plasma circulation of pro-inflammatory and prothrombotic chemokines together with an overtly increased in vulnerability to oxidative stress [7-14]. The decreased plasma nitric oxide levels in obesity further exacerbates the progression of atherosclerotic lesion formation [14].

Cardiovascular diseases are prominent among the various complications of obesity in humans, albeit they usually take many years to develop. Animal models are therefore an indispensable alternative for studying the probable obesity-associated cardiovascular risks associated with the obese condition. Hitherto, rodent models (including spontaneous single-gene loss-of-function mutation, gain-of-function mutation, transgenic model, polygenic models), and others generated from exposure to different environmental conditions have all been employed in the study of obesity [15-18]. However, neither of these models have been found to truly reflect the sequential order of metabolic and morphometric changes that occur in humans with obesity. The need for a more suitable model for the advancement of the study of obese condition cannot be overemphasized.

The aim of this study therefore was to use a high fat diet (HFD) to induce obesity in male Wistar rats as a model to evaluate the zoometric, morphometric and atherogenic risks associated with obesity condition. In this study, we compared the effect of HFD with that of the standard rat chow (SRC) on male Wistar rat population. We measured morphometric indices (e.g. the Lee/Adiposity index) and several biochemical indices (e.g. lipid profile, atherogenic index of plasma (AIP), coronary risk ratio (CRR), atherogenic coefficient (AC), and the atherogenic index (AI)). Finally, we evaluated possible correlations between measured zoometric and atherogenic indices.

Materials and methods

High fat diet formulation

The high fat diet (HFD) was prepared by mixing soya-bean oil and melted pork tallow with commercially-obtained SRC at room temperature to provide 31.25% of the total energy from fat. This mixture was stirred to produce dispersed semi-solid pellets and used for feeding the HFD group. Proximate analysis was undertaken on the feed to determine the proportions of nutrients (proteins, carbohydrate, lipid, and minerals) and energy densities of the HFD and standard chow (Table 1).

Animal care and ethical considerations

In all, 40 male Wistar rats (170 ± 15 g, 8 weeks old) were obtained from the Department of Animal Science, Kwame Nkrumah University of Science & Technology (KNUST) in Kumasi (Ghana) and were randomly distributed into two equal sized groups (n = 20). The test group was fed HFD, while rats in the control group were fed SRC. The rats were housed in metal cages (5 animals per cage) at 28 ± 2 ˚C, under a cycle of 12 hours of light and 12 hours of darkness, with free access to food and water for 10 weeks. The animals were housed and cared for under conditions in accordance with the current National Institute of Health (NIH) Guidelines for the Care of Laboratory Animals [19].

Zoometric measurements

During the 10 weeks period of dietary treatment, the rat's body weight, nose-anal length, body mass index (BMI), and adiposity index were measured weekly. Body weight was measured to the nearest 0.01 g using a digital scale (Shanghai Huachao Industrial Co. Ltd, Shanghai, China). The naso-anal length was measured (to the nearest 0.1 cm) using plastic centimeter ruler (Suzhou Chaosheng Stationery Co. Ltd, Anhui, China). The BMI and adiposity index were determined by calculation from the formula:

$$\text{BMI} = \frac{mass\ of\ rat\ (g)}{(naso-anal\ length)^2} = \ldots\ldots\ldots\ \text{g/cm}^2$$

$$\text{Adiposity Index} = \frac{\sqrt[3]{Body\ mass}}{naso-anal\ length} = \text{cm/g}^3$$

Euthanization

Before the anesthesia, final body weight of animals in each group was recorded. Anesthesia was achieved by intraperitoneal injection of 0.04 mg/g body weight of pentobarbital (Taj Pharmaceutical Ltd, Mumbai, India). About 5 ml of blood was collected by cardiopuncture using disposable syringes (Changzou Standard Medical Devices Co., Xinbei – Changzou, China) into sterile blood sample vacutainers (Becton, Dickinson and Company, Franklin Lakes, New Jersey, USA). Samples were kept still for 1hr to clot, then centrifuged at 3000 g for 5minutes and finally the serum aliquoted into clean eppendorf tubes and stored at –80 °C. After successful cardiopuncture, some of the experimental animals were frail and hence were sacrificed and their cadavers were measured.

Morphometric measurements

Following successful dissection, the wet weights of the vital organs (heart, kidney, liver, pancreas), and the abdominal fat were measured to the nearest 0.01 g using a digital scale (Shanghai Huachao Industrial Co. Ltd, Shanghai, China) and recorded.

Biochemical assays

The serum total cholesterol (TC), HDL, and TG concentrations were measured by semi-automated technique using a commercially available reagent (Fortress Diagnostics©, Antrim, N. Ireland) and the Kenza Max BioChemisTry analyzer (Biolabo Diagnostics, Maizy, France). The serum LDL-C, very low density lipoprotein (VLDL-C), and HDL-C/LDL-C ratio were calculated as below;

$$(1)\ \text{LDL} = \frac{\text{TC}}{\text{HDL}(0.2\ \text{x TG})}$$

$$(2)\ \text{VLDL} = \frac{\text{TG}}{2.2}$$

Nota bene: Equations (1) and (2) are used when TG is measured in mg/dl.

Serum atherogenic indices were calculated as follows [20-24]:

$$\text{Cardiac risk ratio}\ (CRR) = \frac{TC}{HDL - \text{C}}$$

$$\text{Atherogenic index}\ (AI) = \frac{LDL - C}{HDL - C}$$

$$\text{Atherogenic co-efficient}\ (AC) = \left(\frac{TC - HDL}{HDL}\right) or \left(\frac{Non - HDL - C}{HDL}\right)$$

$$\text{Atherogenic index of Plasma}\ (AIP) = log10\left(\frac{TG}{HDL} - C\right)$$

The serum fasting insulin levels were assayed by enzyme-linked immunosorbent assay (ELISA) technique using a commercially available kit according to the manufacturer's instructions (Shanghai Chemical Ltd, Shanghai, China) and 10 µl of serum sample.

Statistical analysis

The data from the study were analyzed using the Prism software version 8.0 (GraphPad software, Boston, USA). All continuous and discrete data were expressed as mean ± standard deviation. For continuous variables, group differences were determined using the student t-test or the one-way ANOVA. The Pearson correlation and logistic regression analysis was used to evaluate the correlation and associations respectively between lipidemic indices, BMI, and atherogenic indices among experimental animal population after the dietary treatment. From the analysis, all p values < 0.05 were considered significant.

Results and discussion

Figure 1 and Figure 2 show marked increases in average weight gain (BMI > 40%) and mean adiposity index (0.35) among the animals fed with HFD for 10 weeks, compared to those fed with SRC. The results are presented as mean ± standard error of the mean and n represents the number of animals in each group (SRC group n = 20, HFD group n = 18), (a) $p < 0.05$ vs SRC group, (aa) $p < 0.01$ vs SRC group, (bb) $p < 0.05$ vs SRC.

Obesity is one of the common findings from reported in various studies involving the treatment of subjects with high fat diets for extended periods [25-30]. Lozano et al., reported significant weight gain among rat population treated with high fat only and high fat and high fructose (HFHF) diets for two months compared to rats rationed on SRC [24]. Despite the strong association established between genes and obesity [31-35] our findings show overtly the influence of an environmental factor (HFD) on weight gain and increased BMI. In other words, long periods of HFD consumption can result in obesity. As expected, our findings from Figure 2M above suggest an average of 40% weight gain probably due to increased abdominal fat accumulation as showed in the elevated adiposity index for the group that received the HFD compared to the controls fed with SRC. Among our study animals, noticeable weight gains were observed from the 3rd week and through to the 10th week of HFD treatment. Diet induced models of obesity (DIO) have been successfully achieved with cafeteria, western, HFHF and cholesterol-rich diets in non-human primates [36-42]. Additionally, findings from our study indicate that HFD consumption over an extended period could be used as a viable alternative for induction of obesity. However, further research will have to be carried out to compare the robustness (or otherwise) of the above alternative models for induction of obesity in non-human primates and their relative suitability for studies relating to the risk factors associated with obesity.

Obesity is implicated as a viable risk factor to a wide spectrum of diseases such as non-alcoholic fatty liver disease (NAFLD), renal insufficiency, obesity-related cardiomyopathy, cancers, immune-suppression, insulin resistance, metabolic syndrome, and diabetes [43-52] From the pathology point of view, increased visceral, subcutaneous, abdominal, and intra-hepatic fat accumulations are a common effect of obesity [53]. Our study findings in Table 2 and Figure 2 above show increased abdominal fat accumulation and elevated body adiposity among the HFD-treated animals compared to those on SRC respectively. This phenotype is associated with marked increase in plasma circulating pro-inflammatory cytokines such as interleukin – 6 and α-tumor necrosis factor (TNF-α) [54-56] The circulating TNF-α provokes induces mitochondrial damage and induces systemic oxidative stress by inducing increased release of reactive oxygen species (ROS), increased expression of TNF-receptor 2 (TNFR-2) and consequent expression of vascular adhesion factors (VCAM-1 and ICAM-1) downstream increasing recruitment, adhesion and infiltration of inflammatory leucocytes hence increasing risk of CAD [57-60] Again, the weight of the various abdominal organs were significantly higher in the obese rats than in controls. This finding further reveals the possible systemic effect of obesity on the vital organs of an organism owing to the significant increase in the gross weights of liver, kidney, heart, and pancreas in the obese rats. While there is sufficient literature correlating obesity with various diseases associated

Table 1. Nutritional composition and proportions of the experimental rats' diet obtained from proximate analysis of SRC and HFD

Composition (p/p)	Standard rat chow (SRC)	High-fat Diet (HFD)
	% weight	% weight
Carbohydrate	41.475	30.500
Protein	18.850	17.475
Fat/lipids	1.975	31.250
Fibre	7.700	8.350
Mineral/vitamins	5.625	5.325
Energy (kCal/kg)	2590.750	4731.500

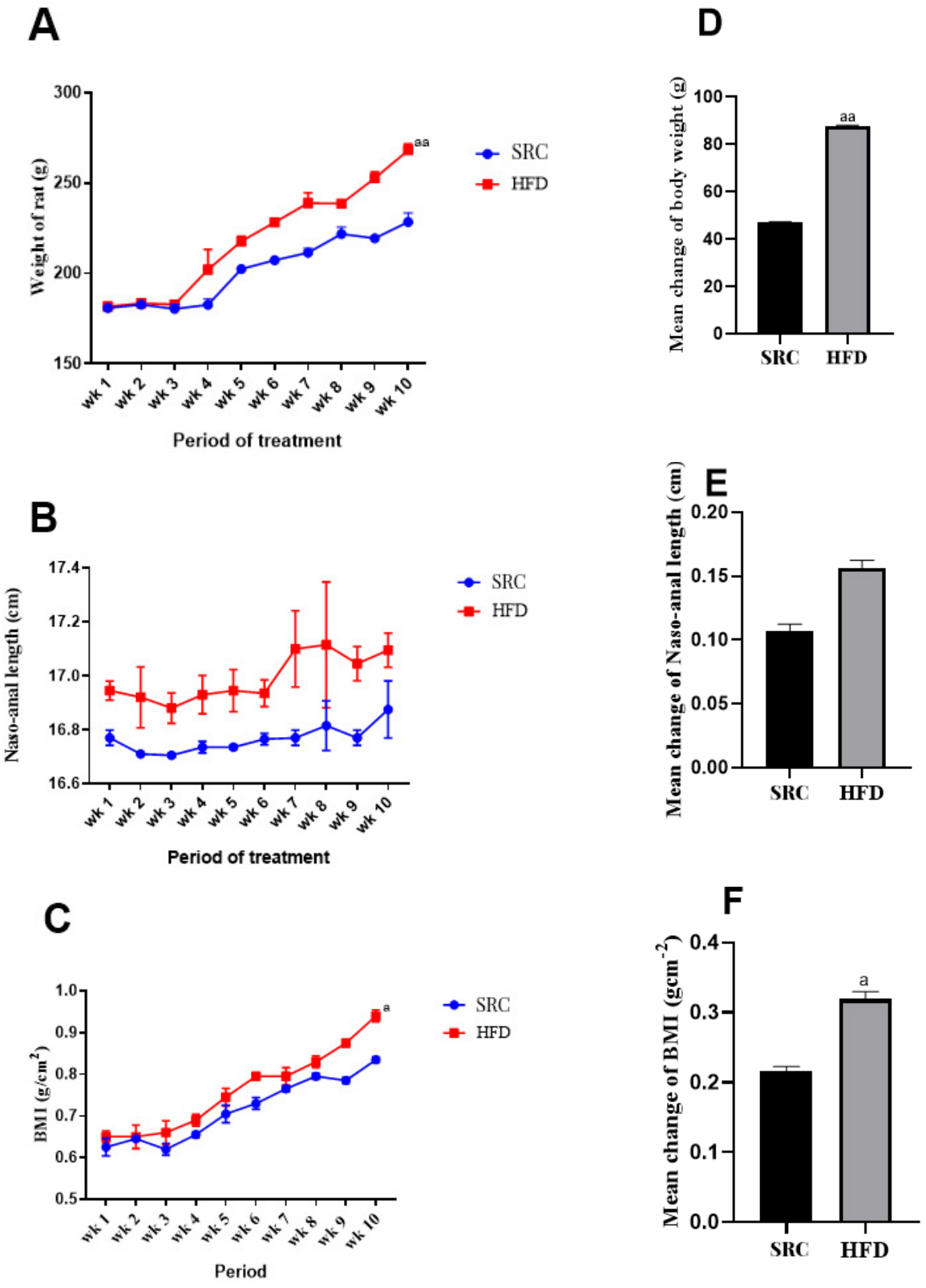

Figure 1. Zoometric measurements of experimental animals
A – body weight evaluation; B – nose-anal length changes; C – body mass index (BMI) evaluation; D – mean change in body weight; E – mean change in nose-anal length; F – mean change in BMI after 10 weeks of dietary treatment; HFD – high fat diet; SRC – standard rat chow

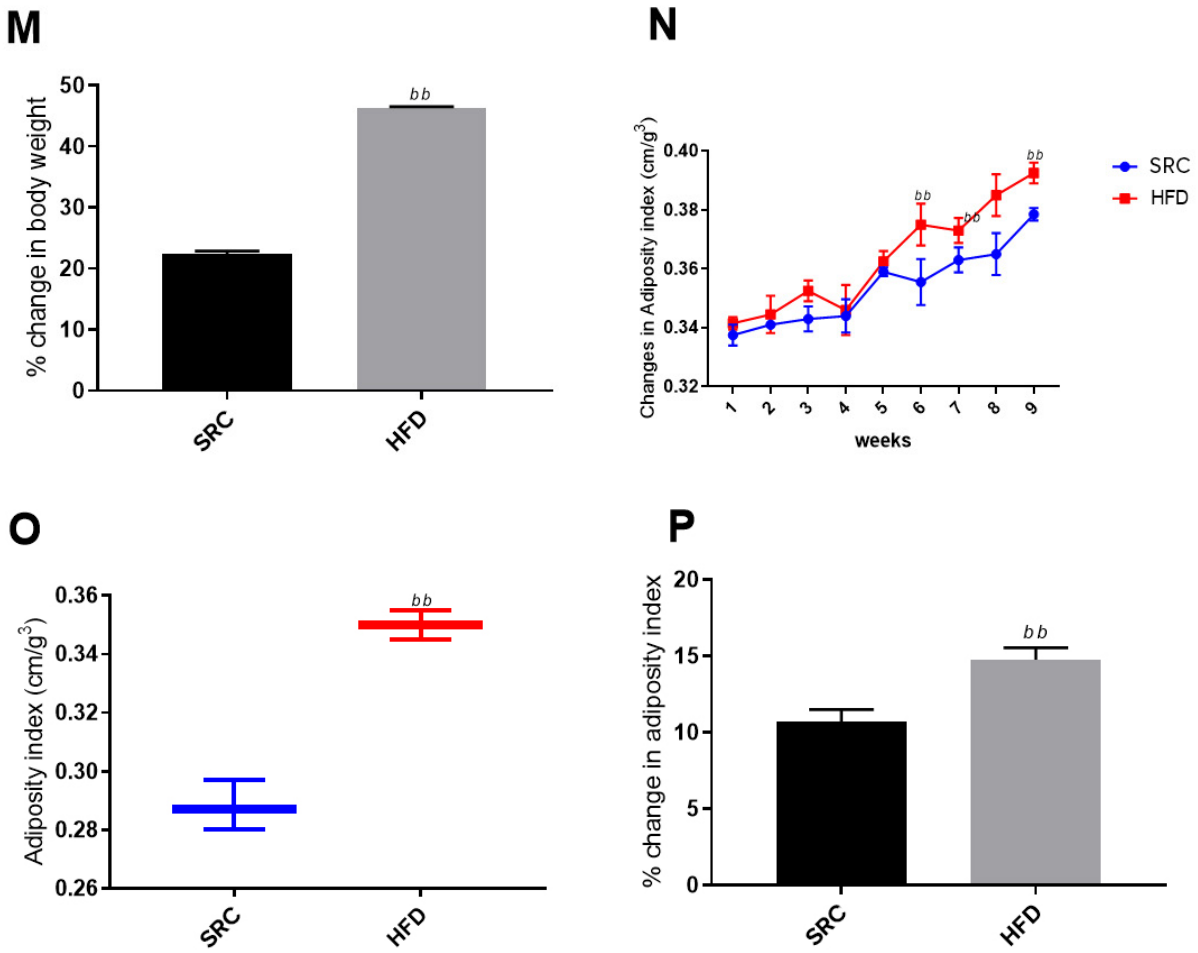

Figure 2. Morphometric measurements of experimental animals
HFD – high fat diet; M – evaluation of percentage body weight; N – change in adiposity index; O – change in adiposity indices; P – percentage change in adiposity index; SRC – standard rat chow

Table 2. Morphometric measurements of Wistar rats after 10 weeks of treatment with SRC and HFD

	SRC (n = 20)	HFD (n = 18)	p-value
Liver weight (g)	5.68 ± 1.41	8.57 ± 3.03[a]	< 0.01
Abdominal fat (g)	0.43 ± 0.27	5.2 ± 1.40[a]	< 0.0001
Kidney weight (g)	0.62 ± 0.25	1.17 ± 0.08[a]	< 0.01
Pancreas weight (g)	0. 69 ± 0.11	1.15 ± 0.45[a]	0.027
Weight gain/pancreas weight	36.2 ± 10.49	63.3 ± 21.57[a]	< 0.001
Adiposity index	0.28 ± 0.08	0.35 ± 0.13[a]	0.042

Results are presented as mean ± standard error of the mean and n represents the number of animals in each group; The p-values were determined using the unpaired t-test, SRC versus HFD. ([a]) $p < 0.05$ was considered significant when compared against the SRC group; HFD – high fat diet; SRC – standard rat chow.

Table 3. Biochemical characteristics of study animals

	BMI (< 0.65 g/cm²) (n = 9)	BMI (0.65-0.70 g/cm²) (n = 16)	BMI (≥ 0.71 g/cm²) (n = 15)	p-value
FBG (mmol/l)	4.3 ± 0.52	4.60 ± 0.28	5.5 ± 0.69[a]	0.028
RBG (mmol/l)	6.20 ± 0.08	6.13 ± 0.45	6.7 ± 0.28	0.076
VLDL-C (mmol/l)	0.16 ± 0.11	0.13 ± 0.08	0.30 ± 0.06[a]	< 0.01
TG (mmol/l)	0.80 ± 0.17	0.65 ± 0.12	1.50 ± 0.83[a]	< 0.01
TC (mmol/l)	2.46 ± 0.13	3.01 ± 0.18	4.68 ± 1.70[a]	0.035
HDL-C (mmol/l)	1.20 ± 0.60	1.50 ± 0.72	1.90 ± 0.59	0.082
LDL-C (mmol/l)	0.44 ± 0.17	1.21 ± 0.05	2.10 ± 0.23[a]	0.017
TG/HDL-C	0.67 ± 0.33	0.43 ± 0.11	0.79 ± 0.29[a]	0.025
CRR	2.05 ± 0.18	2.01 ± 0.58	2.46 ± 0.73	0.069
AIP	−0.176 ± 0.11	−0.366 ± 0.18	−0.102 ± 0.06[a]	0.022
AC	1.05 ± 0.53	1.01 ± 0.17	1.46 ± 0.68[a]	0.0175
AI	0.37 ± 0.04	0.81 ± 0.29	1.11 ± 0.02[a]	0.041

Results are presented as mean ± standard error of the mean and n represents the number of animals used in each group; The p-value was determined by the one-way analysis of variance; $p < 0.05$ was considered significant; (a) p-value < 0.05; AC – atherogenic coefficient; AI – atherogenic index; AIP – atherogenic index of plasma; BMI – body mass index; CRR – cardiac risk ratio; FBG – fasting blood glucose; HDL-c – high density lipoprotein; LDL-c – low density lipoprotein; RBG – random blood glucose; TC – total cholesterol; TG – triglyceride; VLDL-c – very low density lipoprotein cholesterol.

Table 4. Odds ratio (95% confidence interval) of obesity according to the estimated atherogenic indices

Variable	Odds ratio (95% CI)	p-value
AC	65.0 (68 – 648.26)	< 0.001
AIP	6.0 (0.043 – 24.55)	< 0.001
CRR	48 (4.993 – 461.50)	< 0.001
AI	1.0 (2.56 – 229.57)	< 0.001

AC – atherogenic coefficient; AI – atherogenic index (LDL-c/HDL-c ratio); AIP – atherogenic index of plasma; CI – confidence interval; CRR – coronary risk index

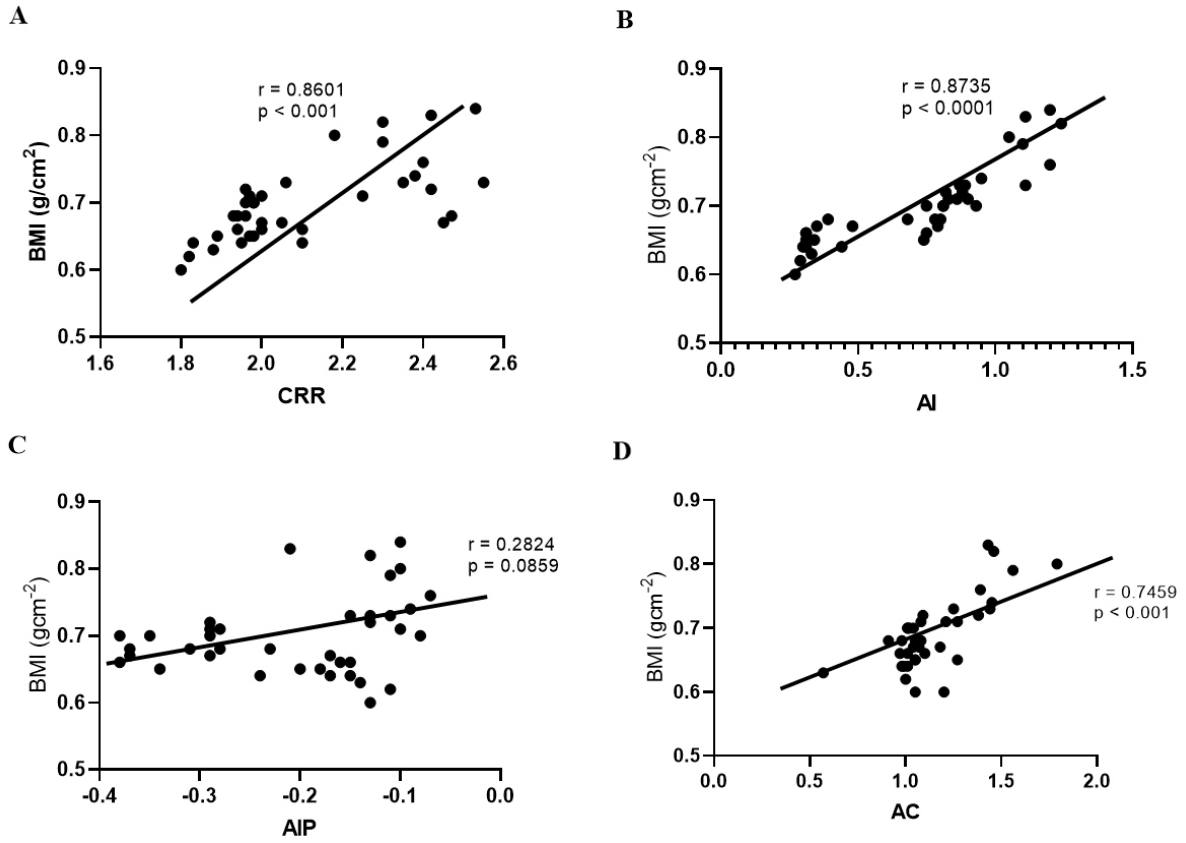

Figure 3. Scatter plot showing significant and positive correlations between different atherogenic indices and increased BMI among experimental animals (r-pearson's coefficient)
From the above figure, the order of increasing strength of correlation among the atherogenic indices with BMI is AIP, AC, CRR, and AI with the strongest positive association (r = 0.28, 0.74, 0.86, and 0.87) respectively. AC – atherogenic coefficient; AI – atherogenic index; AIP – atherogenic index of plasma; CRR – coronary risk ratio

with these organs [61-67] there is rather a paucity of information relating obesity to the function of the kidney, heart, and pancreas. Our findings shown in Tables 1 and 2 provide a justifiable inference for further study into how this change in weight could affect the gross anatomy and function of these organs in obesity.

The atherogenic indices are tools to measure the risk for various forms of coronary artery diseases (CAD)s. Different diseases relate differently to the conventional atherogenic indices. In comprehensive meta-analysis, Wu et al., demonstrated that atherogenic index of plasma (AIP) is independently correlated to CAD among adult population [67]. In another study, AIP, AC, and CRR were implicated in pre-eclampsia among pregnant women [68]. Except for AIP, our findings shown in Table 4 suggest a significant linear relationship between BMI and the principal atherogenic indices namely AC, AI, and CRR. Among them, AI correlated strongly with obesity followed by AC, and CRR with correlation coefficient (r) values of 0.8735 ($p < 0.0001$), 0.7459 ($p < 0.0001$), 0.6811 ($p < 0.0001$) respectively (Figure 3). Notable among our findings is the strong correlation between obesity and the atherogenic indices (Tables 3 and 4). This corroborates the human studies that reported significant increases in atherogenic risks among obese cohorts [69-71]. This further underscores the viability of animal models for studies of human diseases.

Limitations of this study

The animal model we used and the small sample size are a limitation towards extrapolation of our findings to the larger human population. Proximate evaluation of animal diet did not reveal micronutrient distributions which could have played a role in the observed outcomes. Lastly, this experimental study was exploratory and focused primarily on correlational data without exploring the undergirding mechanisms such as oxidative stress, inflammation, insulin resistance among others. Lastly, the 10-week duration of our study was relatively short. Perhaps, a longer duration would have been more appropriate to better explore the effect of diet-induced obesity and coronary artery diseases. These notwithstanding, our findings are consistent with those observed in the human population indicating the usefulness of our model for the further investigations of obesity in humans.

Conclusion

In conclusion, our study corroborates the findings published in various studies that suggest that prolonged consumption of HFD leads to hyperlipidemia and increased cardiovascular risk indicated by increasing several atherogenic indices. This leads to increased vulnerability to heart attack, hypertension, and stroke.

Disclaimer

The findings of this paper are new and solely the responsibility of the authors and do not necessarily represent the official views of any auxiliary agencies.

Conflict of interest

The authors have no conflict of interests regarding the publication of this paper.

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